

Topics in **HIV Medicine**[™]

A publication of the International AIDS Society–USA

Perspectives

Evolving Approaches to Initial Antiretroviral Therapy: 4
When to Start and With What

Roy M. Gulick, MD, MPH

Factors to be Considered in the Decision of When to Initiate Antiretroviral Therapy • Current Recommendations Regarding Initial Regimen Options • Recent Data from Clinical Trials

Drug Resistance Testing in the Management of 10
Antiretroviral Therapy

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About This Issue

June, 2001, marked the 20-year anniversary of the first reported cases of AIDS. Over the past two decades there have been significant contributions to the fight against HIV/AIDS and all of those involved have stories of this fight. In a new addition to *Topics in HIV Medicine*, we will begin to share these stories. This new feature was inspired by Mary Fisher, whose speech given at the New York course last Spring is included in this issue.

In addition, we would like your feedback—we are interested in why you read *Topics in HIV Medicine* and would like to know how we can improve this publication to better meet the needs of our readers. For this reason, we have included a reader survey and ask that you please take a moment to fill it out.

This issue includes 3 *Perspectives* articles, which summarize talks given at the International AIDS Society–USA continuing medical education course series held in Washington, DC, Boston, and San Francisco earlier this year.

Our first article is based on Dr Roy M. Gulick's discussion on when to initiate antiretroviral therapy and current options for initial antiretroviral regimens. The second article summarizes Dr Daniel R. Kuritzkes' review of drug resistance testing in the management of antiretroviral therapy. The third *Perspectives* article provides an overview of Dr Marshall J. Glesby's discussion on the metabolic complications of antiretroviral therapy in relation to coronary artery disease risks.

The next issue of *Topics in HIV Medicine*, available in October, will feature summarized talks given at the 4th Annual HIV Clinical Conference in June, 2001.

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Perspectives

Evolving Approaches to Initial Antiretroviral Therapy: When to Start and With What

Factors to be considered in the decision of when to initiate antiretroviral therapy, current recommendations regarding initial regimen options, and recent data from clinical trials assessing regimen options were discussed by Roy M. Gulick, MD, MPH, at the International AIDS Society–USA course in Washington, DC, in May.

When to Begin

Although there is no longer an emphasis on starting antiretroviral treatment as early in HIV infection as possible, there remains considerable debate regarding when therapy is optimally begun. Factors motivating earlier treatment include the recognition that HIV disease is progressive; the ability of effective therapy to suppress HIV RNA levels, thereby suppressing emergence of resistance, and to increase CD4+ cell counts, thereby improving immune function; and the accumulating data showing that viral suppression can be maintained for a prolonged period (the potential for 5 or more years of suppression has been demonstrated). Arguments for delaying therapy can be based on the low risk of clinical progression in early disease, such practical factors as difficulty in adherence to regimens and the potential for toxicity to outweigh benefits in early disease, and the fact that long-term effects of treatment remain unknown.

Five studies assessing the question of when to begin therapy were reported at the 8th Conference on Retroviruses and Opportunistic Infections this year. In general, the findings of these case-control, observational, or population-based studies support the notion that delaying treatment somewhat is not

associated with a remarkable loss of effect in preventing clinical disease progression.

One exception to this trend in findings is the Swiss HIV Cohort case-control study reported by Opravil and colleagues (8th CROI, 2001). In this study, rates of disease progression in 358 patients beginning antiretroviral therapy between January 1996 and December 1999, with CD4+ cell counts above 350/ μ L, were compared with rates in 358

Starting antiretroviral treatment as early as possible is no longer emphasized, but there remains considerable debate regarding when therapy is optimally begun

HIV-infected patients not receiving therapy who were matched for CD4+ cell count (485/ μ L and 487/ μ L, respectively), age, HIV RNA level (4.26 \log_{10} and 4.10 \log_{10} copies/mL, respectively), and date of enrollment in the cohort. Median durations of follow-up were 2.3 years in the antiretroviral treatment group and 1.3 years in the matched controls, with 14% of the former and 28% of the latter group being lost to follow-up. Instituting therapy at this relatively high CD4+ cell count was associated with highly significant reductions in clinical progression, including reductions in symptomatic disease (Centers for Disease Control and

Prevention [CDC] category B/C) from 17% to 4% ($P < .0001$) and AIDS (CDC category C) from 5% to 1% ($P = .0001$), and a reduction in all-cause mortality from 5% to 1% ($P = .0006$).

Two studies providing evidence of absence of harm in delaying treatment are a CDC observational study reported by Kaplan and colleagues (8th CROI, 2001) and a University of British Columbia population-based study reported by Hogg and colleagues (8th CROI, 2001). In the CDC study, risk of HIV-related death was assessed as a function of CD4+ cell count at the time of starting antiretroviral therapy in 5110 patients observed in the Adult and Adolescent Spectrum of Disease project (a review of medical records in various US cities), who started 2- or 3-drug regimens in 1994 or thereafter. Median follow-up was 1.4 years. Table 1 shows Kaplan-Meier estimates of 2-year survival by CD4+ cell count stratum and the hazard ratio for death in each stratum compared with the $\geq 500/\mu$ L stratum. The hazard ratio for each stratum below 200/ μ L was significantly increased compared with the stratum $\geq 500/\mu$ L. However, no significant increase in hazard ratio was seen for strata within the 200/ μ L to 499/ μ L interval, indicating no significant increase in risk for death among patients beginning therapy at these cell counts compared with counts of 500/ μ L or more for this limited period of time. Limitations of the study include its observational design, short follow-up, absence of evaluation of resistance, and lack of confirmation that patients followed up were antiretroviral-naïve at the start of the study treatment periods.

In the University of British Columbia study, survival was analyzed in patients receiving antiretroviral therapy in the province between January 1996 and September 1999 ($n=1219$) according to CD4+ cell count at initiation of therapy. Median follow-up was 3 years. Survival in those beginning treatment with a

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CD4+ cell count below 350/μL was significantly lower than that in patients starting at counts of 350/μL to 499/μL and in those with counts of 500/μL or more, with no significant difference in rates between the latter groups. It is of interest that stratification by initial HIV RNA level suggested no substantive differences in survival according to pre-treatment viral load.

Recommendations for when to start treatment include those offered by the US Department of Health and Human Services (DHHS; available at <http://www.hivatis.org>) and by the guidelines panel convened by the International AIDS Society–USA (IAS–USA; Carpenter et al, JAMA, 2000). The DHHS recommendations, updated as of April 23, 2001, recommend treatment in patients with CD4+ cell counts below 200/μL, offering of treatment to those with counts of 200/μL to 350/μL, deferral of treatment in those with counts above 350/μL if viral load is less than 55,000 HIV RNA copies/mL, and treatment or deferral in those with counts above 350/μL if viral load is more than 55,000 copies/mL. The IAS–USA guidelines, published in 2000, recommended treatment in patients with CD4+ cell counts below 200/μL and 200/μL to 350/μL.

Recommendations for treatment in those with cell counts above 350/μL were based on viral load as well as clinical and individual patient factors. The IAS–USA panel is currently drafting updated recommendations. A guiding clinical principle, as stated by the May 5, 1999 version of the DHHS guidelines, is that “. . . [T]he patient should make the final decision regarding acceptance of therapy following discussion with the health care provider of specific issues relevant to his/her own clinical situation.”

What to Start With

As of this writing, there are 16 antiretroviral drugs available for use, including 6 nucleoside reverse transcriptase inhibitors (NRTIs), 6 protease inhibitors, 3 nonnucleoside reverse transcriptase inhibitors (NNRTIs), and an investigational nucleotide reverse transcriptase inhibitor available through an expanded access program. Currently the IAS–USA recommends beginning treatment with a regimen consisting of 1 protease inhibitor plus 2 NRTIs, 2 protease inhibitors plus 2 NRTIs, or 1 NNRTI plus 2 NRTIs, with the published guidelines

providing discussion of relative benefits or drawbacks of individual drugs and combinations in these classes. The DHHS recommends combining 1 drug from among efavirenz, indinavir, nelfinavir, saquinavir/ritonavir, indinavir/ritonavir, or lopinavir/ritonavir with one from among the dual nRTI options of stavudine/didanosine, stavudine/lamivudine, zidovudine/didanosine, and zidovudine/lamivudine.

Selection of the initial regimen should be based on a number of factors, including:

- Antiretroviral activity—ie, effects on viral load and CD4+ cell count and clinical response
- Demonstrated durability of response
- Tolerability, including acute adverse effects and risk of chronic adverse effects
- Convenience, including number of pills, dosing interval, and food/fasting requirements
- Potential for preserving future treatment options
- Stage of HIV disease, including consideration of concomitant illnesses and medications and potential drug interactions
- Access and cost

Table 1. Survival and Hazard Ratio for Death According to CD4+ Cell Count at Initiation of Antiretroviral Therapy in Centers for Disease Control and Prevention Observational Study

CD4+ Cell Count Stratum (cells/μL)	Person-Years	Deaths	2-Year Survival	Hazard Ratio	95% Confidence Interval
All	8428	902	81%	NA	NA
0-49	2918	603	65%	5.5	3.0-10.1
50-99	873	114	78%	3.6	1.9-6.8
100-149	734	57	86%	2.7	1.4-5.2
150-199	504	24	90%	2.3	1.1-4.7
200-249	636	27	96%	1.9	0.9-3.8
250-299	541	21	94%	1.9	0.9-3.9
300-349	538	21	93%	1.8	0.9-3.7
350-399	489	11	96%	1.1	0.5-2.4
400-449	372	11	Not estimable	1.5	0.7-3.5
450-499	259	2	98%	0.4	0.1-1.8
≥500	564	11	97%	Reference	Reference

Adapted with permission from Kaplan et al, 8th CROI, 2001.

Three recent studies have examined the effects of preferred nRTI pairs in combination with indinavir in treatment-naïve patients and have found no substantive difference among the combinations. In the START I study (Squires et al, *AIDS*, 2000), viral load of less than 50 HIV RNA copies/mL was achieved in 47% to 49% of patients receiving stavudine/lamivudine/indinavir or zidovudine/lamivudine/indinavir at 48 weeks. In START II (Eron et al, *AIDS*, 2000), viral load of less than 50 copies/mL was achieved at 48 weeks in 35% to 41% of patients receiving stavudine/didanosine/indinavir or zidovudine/lamivudine/indinavir. In Oz-Combo-1 (Carr et al, *AIDS*, 2000), viral load of less than 50 copies/mL was achieved with stavudine/lamivudine/indinavir, zidovudine/lamivudine/indinavir, and stavudine/didanosine/indinavir in 58% of patients at 12 months. Larger studies may be better equipped to evaluate smaller differences among the dual nRTI combinations.

Other recently reported data provide some indication of the duration of effect achieved with preferred regimens. It is important to note that the virologic results described here generally cannot be compared among studies, since the studies were performed in patient populations with different characteristics and did not always employ the same viral load assay or method of analysis. When used in combination with dual nRTIs,

viral load levels of less than 50 HIV RNA copies/mL were achieved in:

- 56% of patients receiving efavirenz at 2 years (intent-to-treat [ITT] population; Levy et al, 8th CROI, 2001)
- 65% of patients receiving indinavir at 3 years (ITT population; Gulick et al, *Ann Intern Med*, 2000)
- 60% of patients receiving nelfinavir at 2 years (on-treatment population; Petersen et al, 7th Eur Conf Clin Aspects Treatment HIV Infect, 1999)
- 66% of patients receiving ritonavir/indinavir at 48 weeks (method of analysis not specified; Boyd et al, 8th CROI, 2001)
- 78% of patients receiving lopinavir/ritonavir at 2 years (ITT population; Stryker et al, 2000)

In addition, viral load of less than 200 copies/mL was achieved in 55% of patients receiving ritonavir/saquinavir at 3 years (ITT population; Cameron et al, 7th CROI, 2000). It is encouraging that these regimens are capable of maintaining viral suppression in many patients for extended periods; nevertheless, our knowledge of duration of effect is very limited for what must be considered life-long treatment.

A number of factors may be considered in deciding whether initial treatment should consist of a protease inhibitor or an NNRTI in combination

with dual nRTIs. Protease inhibitor-based regimens have been assessed in trials in treatment-experienced patients and those with advanced HIV disease, including clinical end point trials, whereas NNRTI-based therapy has been assessed primarily in treatment-naïve patients or those with earlier-stage disease. Follow-up terms now exceed 5 years with protease inhibitor-based regimens and 2 years with NNRTI-based regimens. The 2 drug classes and individual drugs therein are associated with different acute and chronic adverse effects. Protease inhibitors have a higher barrier to resistance, with accumulation of more resistance mutations generally being necessary for virologic breakthrough, compared with the high-level resistance that can be seen with single mutations in the case of NNRTIs. Initial use of protease inhibitor-based regimens spares NNRTI-based regimens for future use and vice versa. NNRTIs generally are easier to take than protease inhibitors in terms of numbers of pills, interval of dosing durations, and food restrictions.

A number of recent studies have compared the virologic effects of regimens recommended for initial therapy. In the Danish Protease Inhibitor Study (Katzenstein et al, *J Infect Dis*, 2000), 318 protease inhibitor-naïve patients (46% antiretroviral-naïve) with baseline viral load of 52,400 copies/mL and CD4+ cell count of 176/ μ L were randomized to treatment with 2 nRTIs (chosen individually) plus open-label indinavir, ritonavir, or ritonavir/saquinavir (400/400 mg bid). The initial report of 24-week findings in this study had indicated superiority in viral load suppression with the ritonavir/saquinavir-based combination. However, at 72 weeks, no significant differences between treatments were seen with regard to proportions of patients with viral load of 20 or fewer copies/mL (ITT analysis; Figure 1).

In the Abbott 863 study, 653 antiretroviral-naïve patients with viral load of more than 400 copies/mL and any CD4+ cell count were randomized to double-blind treatment with stavudine/lamivudine plus either lopinavir/ritonavir or nelfinavir (Johnson et al, 5th Int Cong Drug Ther HIV Infect, 2000). At 48 weeks, viral load of less than 400 copies/mL was achieved in a significant-

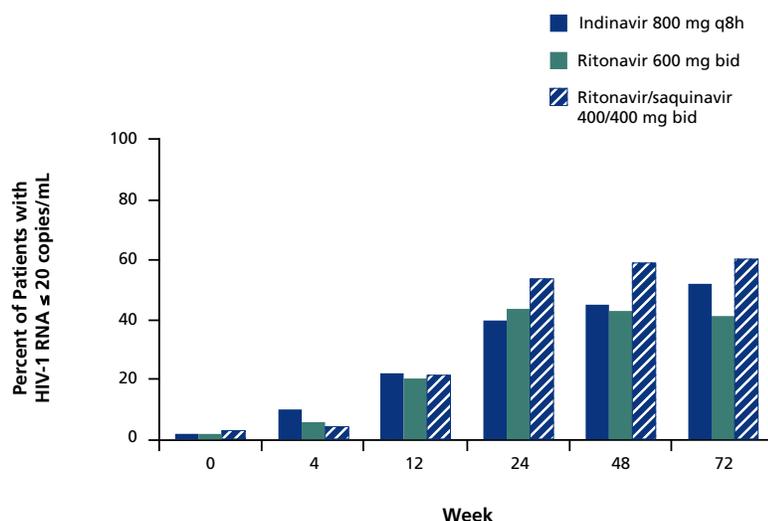


Figure 1. Danish protease inhibitor study: Proportion of patients receiving dual nRTIs plus indinavir, ritonavir, or ritonavir/saquinavir with viral load \leq 20 HIV RNA copies/mL over 72 weeks. Adapted with permission from Katzenstein et al, *J Infect Dis*, 2000.

ly greater proportion of patients receiving lopinavir/ritonavir on ITT analysis.

In the DuPont 006 study, 1266 patients naive to protease inhibitor, lamivudine, and NNRTI treatment with viral load of 10,000 or more copies/mL and CD4+ count of 50 cells/ μ L or more were randomized to open-label treatment with efavirenz/zidovudine/lamivudine, indinavir/zidovudine/lamivudine, or efavirenz/indinavir (Levy et al, 8th CROI, 2001). A greater proportion of patients in the efavirenz/zidovudine/lamivudine group initially responded with viral load reduction to less than 50 copies/mL and a greater proportion remain at this level of response over 96 weeks of treatment. One criticism of this study is that there was a disproportionate dropout rate in the indinavir/zidovudine/lamivudine group early in the study.

Finally, in a pilot study (Boyd et al, 8th CROI, 2001), 104 zidovudine-experienced patients with baseline viral load of approximately 10,000 copies/mL and CD4+ cell count of 168/ μ L received open-label zidovudine/lamivudine plus either indinavir (800 mg tid) or indinavir/ritonavir (800/100 mg bid). At 48 weeks, 66% to 70% of patients receiving these regimens had viral load of less than 50 copies/mL.

In addition to the suggested or preferred initial regimens, a number are considered to be under evaluation, including triple nRTI regimens and regimens consisting of 1 protease inhibitor, 1 NNRTI, and 1 nRTI. Triple nRTI regimens may be the easiest to take (eg, the coformulated lamivudine/zidovudine/abacavir can be taken as 1 pill twice daily) and may be associated with fewer drug interactions than other regimens, in addition to sparing protease inhibitor- and NNRTI-based regimens for later use. There are no clinical end point data for such regimens, long-term virologic effects have yet to be defined (there is some concern regarding magnitude of response at higher initial viral loads), and there is some concern that possible nRTI-associated mitochondrial toxicity could be exacerbated with triple combinations. In addition, there are theoretical drawbacks to targeting a single step in the viral replication cycle.

A number of recent trials examining triple nRTI regimens have been report-

ed. In the CNA 3005 study (Staszewski et al, JAMA, 2001), 562 treatment-naive patients with a baseline viral load of approximately 65,000 HIV RNA copies/mL and CD4+ cell count of 360/ μ L were randomized to double-blind treatment with zidovudine/lamivudine and either abacavir or indinavir. On ITT analysis, there was no difference between groups with regard to proportion of patients with viral load of 50 copies/mL or less at week 48 (40% in abacavir group and 46% in indinavir group). However, among patients with baseline viral load of more than 100,000 copies/mL, a significantly greater proportion of indinavir patients had viral load of 50 copies/mL or less (45% vs 31%).

Initial regimens
under evaluation
include 3 nRTI regimens
and 1 nRTI /
1 NNRTI / 1 protease
inhibitor regimens

In the CNAB 3014 study (Cahn, XIII Int AIDS Conf, 2000), 342 antiretroviral-naive patients were randomized to treatment with the same triple regimens as in CNA 3005; however, treatment was open-label, permitting the abacavir regimen to be given in 2 daily doses and without the fasting and fluid restrictions required for indinavir administration. At baseline, median HIV RNA was 62,000 copies/mL in the abacavir group and 73,000 copies/mL in the indinavir group; median CD4+ cell count was 312/ μ L and 298/ μ L, respectively. At 24 weeks, viral load of less than 400 copies/mL was achieved in 87% of the abacavir group and 83% of the indinavir group on as-treated analysis and in 68% of the abacavir group and 57% of the indinavir group on ITT analysis. Updated results presented at the First International AIDS Society Conference on HIV Pathogenesis and Treatment in July showed HIV-1 RNA

of less than 400 copies/mL in 66% of the abacavir group versus 50% of the indinavir group at week 48 (ITT analysis, missing data equals failure; Vibhagool et al, 2001).

Finally, the Atlantic study (Squires et al, XIII Int AIDS Conf, 2000) assessed effects of combining stavudine/didanosine with indinavir, nevirapine (once daily), or lamivudine in open-label treatment of 298 treatment-naive patients with baseline viral load of approximately 18,000 copies/mL and CD4+ cell count of 406/ μ L. At 48 weeks, viral load of less than 50 copies/mL was achieved in 49% of the indinavir group, 49% of the nevirapine group, and 40% of the lamivudine group on ITT analysis.

Several large ongoing studies will provide additional data to help answer the question of what to start with, including two AIDS Clinical Trials Group (ACTG) studies from which data are expected to be available in the near future. In ACTG 384, nearly 1000 treatment-naive patients with HIV RNA levels above 500 copies/mL have been randomized to lamivudine/zidovudine (fixed-dosage) or didanosine/stavudine plus efavirenz or nelfinavir or both. Patients with virologic failure are crossed over to an alternative study regimen. Scheduled follow-up in the study, which is near completion, is 2 or more years. This study may indicate which of the double nRTI regimens is superior for starting and whether an NNRTI, protease inhibitor, or both should be added for initial and subsequent treatment. In ACTG 388, 517 patients with advanced HIV disease (baseline HIV RNA level >80,000 copies/mL and CD4+ cell count <200/ μ L), have been randomized to lamivudine/zidovudine plus indinavir, indinavir/efavirenz, or indinavir/nelfinavir, with planned follow up of 2 or more years. Recent preliminary results suggest that the 4-drug regimen of zidovudine/lamivudine plus indinavir/efavirenz had a superior virologic response rate. The INITIO study (Europe, Canada, Australia) and the FIRST study (CPCRA 058) are large studies currently in progress that are exploring the optimal initial regimen.

Initial regimens may need to be altered for reasons other than virologic failure, including adherence problems

and toxicity. Current and future options in changing drugs for adherence reasons include new coformulated combinations and improved drug forms that reduce pill number and that permit once-daily dosing. Available coformulated combinations consist of lamivudine/zidovudine, lamivudine/zidovudine/abacavir, and lopinavir/ritonavir. With regard to improved formulations that reduce the number of required pills, delavirdine is now available in a 200 mg form; a 600 mg form of efavirenz and a 625 mg form of nelfinavir currently are in development. With regard to number of doses, didanosine can now be given once-daily in the newly approved didanosine enteric-coated form. A zidovudine sustained-release form and a stavudine extended-release form, which would permit once-daily dosing, are in development. Efavirenz is dosed once daily, and nevirapine, lamivudine, lopinavir/ritonavir, indinavir/ritonavir, saquinavir/ritonavir, and amprenavir/ritonavir each has potential for once-daily dosing. Investigational agents that permit once-daily dosing include the amprenavir prodrug GW 908 with ritonavir, emtricitabine, tenofovir, and the protease inhibitor atazanavir (BMS-232632). Dosing interval or number of pills required can be reduced with use of ritonavir or delavirdine as a pharmacokinetic enhancer.

A number of options are available for altering regimens due to toxicity. In some cases, instituting dose reductions for the nRTIs zidovudine, didanosine, and stavudine, or for ritonavir, may be useful, though reduced antiretroviral activity may be an issue. In addition there is a greater degree of comfort with within-class substitutions, including substitutions among protease inhibitors, substitutions among NNRTIs, and substitutions between stavudine and zidovudine or between didanosine and abacavir among the nRTIs. Class switches can also be considered—eg, from a protease inhibitor to an NNRTI- or abacavir-based treatment (please see page 18 in the accompanying article on metabolic complications for more information on switching drugs).

Summary

The optimal time to begin antiretroviral therapy remains unclear, as does the

optimal form of initial therapy. With regard to the latter, currently recommended choices include combining 1 protease inhibitor (or 2 protease inhibitors) or 1 NNRTI with 2 nRTIs. Individualization of therapy based on patient circumstances is the primary clinical principle of treatment. Changes in initial regimens may be required due to adherence and tolerability issues, as well as due to virologic failure. Further research will help define optimal approaches to initial treatment.

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Suggested Reading

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Update on Drug Resistance Mutations

A subgroup of the International AIDS Society–USA Panel on Resistance Testing Guidelines is regularly monitoring new research efforts and updating its list of drug resistance mutations originally published in 1998 and 2000 (Hirsh et al, JAMA). Under the leadership of Drs Richard T. D’Aquila and Jonathan M. Schapiro, the subgroup updated the list in May, 2001 (published

in the June, 2001 issue of *Topics in HIV Medicine*) and will issue another update in September on the International AIDS Society–USA Web site (<http://www.iasusa.org>). The September update will incorporate new data presented at the 5th International Workshop on Drug Resistance and Treatment Strategies in June in Scottsdale, Arizona.

Perspectives

Drug Resistance Testing in the Management of Antiretroviral Therapy

Daniel R. Kuritzkes, MD, discussed aspects of genotypic and phenotypic resistance testing, and virologic results achieved with treatment guided by testing in clinical studies, at the International AIDS Society–USA course in Boston in March.

Antiretroviral resistance due to HIV-1 mutations develops differently among different drug classes and can evolve via different pathways for specific drugs. For some drugs, such as lamivudine and the nonnucleoside reverse transcriptase inhibitors (NNRTIs), single point mutations can rapidly confer high-level resistance. For others, such as zidovudine and protease inhibitors, high-level resistance requires 3 or more mutations within a single genome. Continued use of drugs in a failing regimen results in an accumulation of mutations in addition to those initially conferring resistance, indicating continued viral adaptation to growth in drug presence and resulting in greater levels of resistance and conferral of increased cross-resistance to other members of the drug class.

Mutational pathways to resistance are difficult to predict and are associated with different resistance patterns. For zidovudine, for example, resistance mediated by the codon 215 mutation (in conjunction with other mutations) also confers resistance to the thymidine analogue stavudine; resistance mediated by the Q151M mutation confers multinucleoside resistance excluding the investigational nucleotide reverse transcriptase inhibitor (nRTI) tenofovir, and resistance mediated by the insertional mutation at codon 69 confers multinucleoside resistance excluding the investigational nucleoside reverse transcriptase inhibitor (nRTI) DAPD. Although it was once thought that evolution of nel-

finavir resistance was relatively straightforward, it is now known that whereas the more commonly observed D30N mutation is associated with narrow nel-finavir resistance, resistance mediated by the L90M mutation (observed in some 10% to 15% of cases) is associated with resistance to saquinavir, indinavir, and other protease inhibitors. Similarly, narrow resistance to amprenavir is conferred by the I50V mutation (often accompanied by the M46I and I47V mutations), whereas multidrug resistance among protease inhibitors is conferred by the I84V amprenavir-associated resistance mutation.

Along with difficulty in predicting mutation pathways, the increasing frequency of transmission of drug-resistant virus is an important factor motivating clinical use of resistance testing. Data on phenotypic resistance (defined as >10-fold resistance on phenotypic assay) of virus from recently infected patients at a number of centers in 1999 to 2000 indicate that compared with sensitivities in 1995 to 1998, rates of any antiretroviral resistance increased from 3.5% to 14% ($P = .001$). This included increases in nRTI resistance from 2.7% to 8.2% ($P = .03$), in NNRTI resistance from 1.3% to 7.1% ($P = .007$), in protease inhibitor resistance from 0.4% to 8.2% ($P = .001$), and in resistance to 2 or more drugs from 0.4% to 5.8% ($P = .002$; Little et al, 8th CROI, 2001).

Assays for Drug Resistance

Drug resistance can be assessed by genotypic assay or phenotypic assay. Currently, genotypic assays determine the presence or absence of specific changes in HIV-1 protease and reverse transcriptase genes, since these enzymes are the targets of currently available drugs. Assays will eventually have to incorporate viral envelope genes as fusion inhibiting drugs make their way into clinical use. Genotyping is

widely available and is performed by several different methods. Since genotypic assays simply indicate whether mutations are present or not and do not indicate how the virus examined behaves in the presence of drug, resistance is inferred by the presence of known resistance mutations; use in clinical practice thus presupposes knowledge of important resistance mutations for particular drugs.

Phenotypic assays measure the 50% or 90% inhibitory concentration (IC_{50} , IC_{90}) for a drug by recombinant virus assay. These assays are currently performed by only 2 laboratories. They can reliably detect changes in susceptibility of as small as 2.5-fold. In brief, the assays are performed by extracting HIV-1 RNA from a plasma sample, which is then converted to complementary DNA by reverse transcription in the test tube. The DNA is then amplified by polymerase chain reaction (PCR); the proximity of the reverse transcriptase and protease genes allows performance of a single PCR reaction generating a single amplicon. This material can be sequenced for reverse transcriptase and protease genotype. For phenotype analysis, the pooled amplicons, reflecting the diversity of genetic sequences present in circulating virus, are introduced into plasmids by recombination or site-specific cloning to form infectious HIV-1 clones that contain the same envelope and regulatory sequences for each patient specimen. Infectious virus generated by these procedures is then tested for drug susceptibility in an automated assay format, yielding inhibition curves from which inhibitory concentrations can be calculated.

Use of resistance assays is complicated by a number of factors. In general, plasma samples with more than 500 to 1000 HIV-1 RNA copies/mL are needed to generate results. In addition, virus species constituting less than 20% to 30% (even as high as 50%) of the amplified product may not be detected. The

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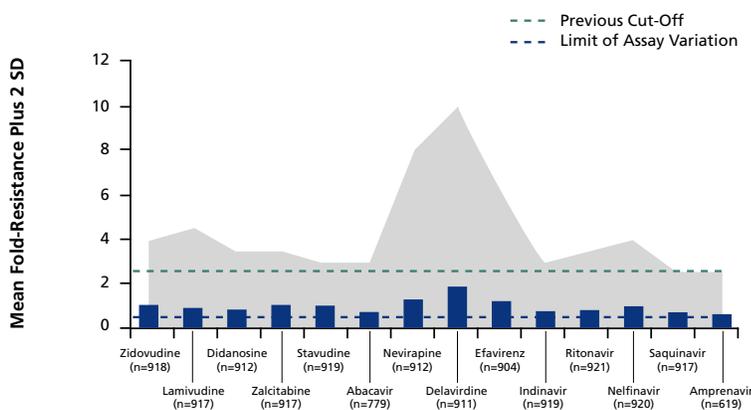


Figure 1. Comparative phenotypic variation among antiretrovirals using drug-naive patient samples. SD indicates standard deviation. Adapted with permission from Graham et al, 8th CROI, 2001. Courtesy of Virco, Mechelen, Belgium.

results from the predominant species may thus not reflect important minority populations. Moreover, false-positive and false-negative results can be generated during PCR due to contamination from prior samples or random polymerase errors. With regard to genotypic assays, interpretation of results is limited by incomplete knowledge of the mutations associated with resistance and by lag in availability of data coordinating particular mutations with resistance. A number of sources provide interpretations of genotypic findings that are updated at variable intervals, and interpretation at any given time may thus rely on outdated data. With regard to phenotypic assays, changes in susceptibility do not necessarily imply resistance or predict clinical response to a given drug; resistance is best considered as a combination of the intrinsic susceptibility of the virus to the drug, the achievable concentration of the drug in the host, and the interaction of pharmacologic and virologic factors that lead to clinical response or lack thereof. Clinically relevant breakpoints for most drugs have yet to be established.

Some of the limitations of the resistance assays are demonstrated by cases arising in clinical practice in which genotypic and phenotypic data are at apparent odds. In one case described by Dr Kuritzkes, genotypic analysis suggested the presence of didanosine resistance, based on a codon 74 mutation, lamivudine susceptibility, based on absence of the codon 184 mutation, and

stavudine susceptibility. Phenotypic assay results showed borderline susceptibility to didanosine and resistance to both lamivudine and stavudine. In this case, interpretation of genotypic findings by the laboratory performing the assay was based on data that did not yet reflect recognition of mutations arising in the context of long-term zidovudine treatment that can confer cross-resistance to lamivudine. In another case, virus judged to be phenotypically sensitive to zidovudine was found to have all 5 of the major zidovudine-resistance mutations. However, the virus also contained the 184V resistance mutation to lamivudine, which resulted in reversion to phenotypic zidovudine susceptibility.

Work is ongoing to refine interpretation of findings on both types of assays. Until recently, any virus showing a higher than 2.5-fold variation in susceptibility compared to wild-type reference strain was considered resistant, although it was recognized that there must be naturally occurring interstrain differences in susceptibility. Data have been collected using large numbers of drug-naive patient samples that show the magnitude of phenotypic variation for different drugs. These data have allowed new cut-off values for phenotypic resistance to be formulated. As shown in Figure 1, the range of variability for NNRTIs was found to be quite large compared with nRTIs and protease inhibitors (Graham et al, 8th CROI, 2001).

More important than the establish-

ment of cut-off values based on phenotypic variation is the correlation of phenotypic resistance with virologic response. An attempt has been made to identify clinical breakpoints for some agents. Analysis of the effects of the addition of abacavir as a single drug to existing regimens in early trials of the drug showed that in the majority of patients, there was a more than 0.5 log-decrease in plasma HIV-1 RNA in the context of 0- to 4.5-fold abacavir phenotypic resistance (Lanier et al, 8th CROI, 2001). Fewer patients exhibited a decrease of this magnitude at 4.5- to 6.5-fold resistance, with very few achieving such a reduction at more than 6.5-fold resistance. Based on these findings, a 4.5-fold change in susceptibility was selected as the susceptibility breakpoint.

Analysis of the effects of adding lopinavir and an NNRTI to failing protease inhibitor-based regimens in multiple protease inhibitor-experienced patients showed virologic response (<400 HIV-1 RNA copies/mL) in 93% of patients with less than 10-fold phenotypic resistance to lopinavir at baseline (Kempf et al, 4th Int Workshop HIV Drug Resistance Treatment Strategies, 2000). Although this level of resistance was selected as the clinically relevant cut-off for susceptibility, patients still exhibited response at higher-fold resistance levels, with the degree of contribution of the NNRTI to this response being unclear. The abacavir and lopinavir data serve to support the notion that there is not likely to be a rigid cut-off value defining resistance to any single drug, but rather a gradient of likelihood of response that is proportional to the level of resistance.

One attempt currently being made to improve utility of genotypic findings is the development of an interpretive system based on derivation of a virtual phenotype from the genetic sequences in patient samples. The systems currently used for interpreting genotype data can be considered rules-based, using databases that require frequent updating as new data become available. Attempts are now being made to devise "intelligent" systems using neural networks that provide data-driven correlations between genotypes and phenotypes that can be updated in real time. In this virtual phenotype approach, samples from a large database (currently

approximately 20,000 samples) of paired phenotypes and genotypes are queried for “matches” to a patient sample genetic sequence. An average phenotype is calculated based on the actual phenotypes of the matching genetic sequences identified in the database. Based on this virtual phenotype, the test genetic sequence is characterized as susceptible or resistant, with the number of matches and the distribution of susceptible and resistant isolates among the matching set being reported. The results of this analysis thus basically provide a probability of susceptibility or resistance.

For example, for a clinical sample with multiple zidovudine resistance mutations and no 184V lamivudine resistance mutation, results indicated that the virus was likely to be zidovudine-resistant, with an average of 30-fold resistance among the matching set, although 10% of the matches were categorized as zidovudine-susceptible. The average resistance to lamivudine was 3.3-fold, with 55% of matches being resistant and 45% susceptible. This virtual phenotype approach is associated with a number of advantages, including reduction of the complex genotypic data to simple categories, interpretation based on actual data from a growing set of samples, and the provision of a measure of robustness of the data. However, the simplicity of results may be misleading, particularly in cases in which the matching set is small, and strength of correlations from the matched sample pool will be weaker for new drugs and for rare viral variants.

Use of Resistance Data in Clinical Studies

Despite the limitations of the resistance assays, retrospective studies have shown that pretreatment genotype or phenotype is significantly predictive of virologic response and prospective studies have shown that treatment based on assay data is associated with improved virologic outcome. A meta-analysis of retrospective genotype and phenotype studies by the Resistance Collaborative Group (DeGruttola et al, *Antivir Ther*, 2000) showed that (1) the likelihood of virologic failure was reduced by 30% to 50% for each drug in salvage regimens to which the assay predicted susceptibility,

with the predictive effect being significant in most of the individual studies, and (2) prediction of drug resistance was an independent risk factor for treatment failure.

Among prospective studies, the VIRADAPT study (Durant et al, *Lancet*, 1999) in patients in whom a protease inhibitor-containing 3-drug regimen was failing showed that 32.3% of patients having genotype analysis versus 14.0% of those receiving standard care had virologic response (viral load <200 copies/mL) at 6 months. Although this difference fell short of statistical significance, overall reduction in viral load was significantly greater in the genotyping group. In the GART study in patients in whom 3-drug combination regimens were failing, genotyping plus expert advice resulted in significant reductions in viral load over 12 weeks compared with usual care (Baxter et al, *AIDS*, 2000). The proportion of patients with virologic response (HIV-1 RNA <500 copies/mL) was also significantly greater in the genotyping plus advice group. In the recently reported Havana trial, patients in whom antiretroviral therapy was failing were assigned in factorial fashion to genotyping or no genotyping with or without expert advice. Intent-to-treat analysis showed that the genotyping/advice group had a significantly greater reduction in viral load at 24 weeks (1.3-log reduction, $P = .015$) than did the other groups (Figure 2). The reduction in the genotype/no advice group (1.0 log) was greater than those in

the no genotype/advice and no genotype/no advice groups (0.8 log in both; Tural et al, 40th ICAAC, 2000).

A recent analysis of cost-effectiveness of genotypic resistance testing showed that such testing was highly cost effective when it produced reductions in virologic failure rates of the magnitude observed in the VIRADAPT and GART studies (25%-38%; Weinstein et al, *Ann Intern Med*, 2001). In fact, given the high cost of antiretroviral therapy and the cost-savings that would result from sparing use of ineffective drugs, it was calculated that genotypic testing would still be cost-effective at a cost of \$10,000 per test.

The VIRA3001 study examined the utility of phenotypic resistance testing in patients in whom the first protease inhibitor-containing regimen was failing. Study results showed that patients receiving salvage treatment based on phenotypic assay results had a significantly greater reduction in viral load at week 16 compared with those receiving standard care (1.27 log versus 0.75 log, $P = .005$) (Cohen et al, XIII Int AIDS Conf, 2000). A significantly greater proportion of the patients in the phenotype group had a reduction in viral load to less than 400 copies/mL. In the NARVAL study, patients in whom a 3-drug protease inhibitor-containing regimen was failing received standard care, treatment based on genotypic testing, or treatment based on phenotypic testing. On final analysis, there were no significant differences among groups at 12 weeks in

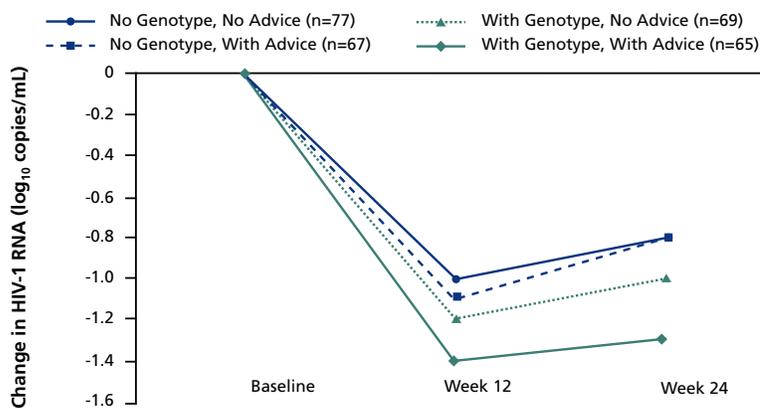


Figure 2. Changes in plasma HIV-1 RNA level in HAVANA study according to whether patients had genotyping or not with or without expert advice. Adapted with permission from Tural et al, 40th ICAAC, 2000. Courtesy of B. Clotet, MD, PhD.

terms of proportions of patients with viral load reduced to below 200 copies/mL. However, an exploratory secondary analysis showed a significant difference among groups with regard to proportions of patients achieving such response at both 12 and 24 weeks, with the proportion of responders in the genotype group being significantly greater than that in the standard care group (29% vs 17%). Differences between these groups was more marked in patients with lower initial viral loads and in those with minimal prior treatment experience (Meynard et al, *Antivir Ther*, 2000).

The finding in the NARVAL study that resistance testing was not associated with any marked improvement in outcome in heavily pretreated patients is not surprising, given that such patients may have few or no treatment options available. In such cases, resistance testing may still prove useful, since it may provide guidance in removing drugs that are not working from the treatment regimen. However, it is important to note that there may still be advantages to continuing failing antiretroviral regimens in patients with few or no remaining options if partial viral suppression can be maintained.

The concept of inhibitory quotient—which characterizes the relationship between drug exposure and susceptibility of a pathogen—has begun to be applied to prediction of response to protease inhibitor therapy. Protease inhibitor therapy is a suitable candidate for such an endeavor, since protease inhibitor plasma levels can be altered by pharmacologic enhancement. With inhibitory quotient defined as trough drug plasma concentration divided by drug IC_{50} , the inhibitory quotient of lopinavir was found to predict response to lopinavir plus efavirenz and nRTI therapy in multiple protease inhibitor-experienced/NNRTI-naive patients. In another study, indinavir-experienced patients received indinavir plus ritonavir. Plasma HIV-1 RNA levels were maintained at less than 50 copies/mL at 48 weeks in 80% of patients with an indinavir inhibitory quotient of more than 2 (ie, trough concentration at least twice the IC_{50}) compared with 0% of patients with a quotient of less than 2 (Kempf et al, 8th CROI, 2001).

Current Recommendations for Use of Resistance Testing

Available data provide a compelling rationale for use of resistance testing in managing antiretroviral therapy despite its acknowledged current limitations. Resistance testing currently is recommended in patients experiencing antiretroviral regimen failure and in pregnant women, in whom it should be used to assist in maximizing viral suppression. It should be considered for use in patients with primary infection and before starting therapy in patients in areas of high prevalence of transmission of resistant virus, including patients from such areas with chronic established infection.

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Perspectives

Metabolic Complications of Antiretroviral Therapy: Coronary Artery Disease Risks

Coronary artery disease (CAD) risk factors have been increasingly observed in HIV-infected patients receiving potent antiretroviral therapy, although such risk factors were also detected in patients prior to use of potent combination regimens. Risk factor profiles, epidemiologic data on risk of CAD clinical events, and risk assessment and management were discussed by Marshall J. Glesby, MD, PhD, at the San Francisco course in April.

In 1998, Henry and colleagues (*Lancet*) reported 2 cases of myocardial infarction in young men with HIV disease receiving protease inhibitor-including antiretroviral therapy. The report of these cases was followed by more than a dozen additional case reports, generating considerable concern about accelerated atherosclerosis in HIV-infected patients receiving potent antiretroviral therapy. Coronary artery disease (CAD) risk has thus recently emerged as an important clinical concern; Dr Glesby noted, however, that cardiac involvement is relatively common in advanced HIV infection (including pericardial effusion, endocarditis, and cardiomyopathy), and that CAD risk factors and atherosclerosis were described in HIV-infected patients in the early years of the epidemic.

Reports of risk factors prior to the era of potent antiretroviral therapy include observation of hypertriglyceridemia and decreased high-density lipoprotein (HDL) cholesterol levels (Grunfeld et al, *Am J Med*, 1989); increased plasma levels of endothelial cell products (eg, von Willebrand factor, tissue plasminogen activator; Lafeuillade et al, *J Acquir Immune Defic Syndr*, 1992); and vascular endothelial damage and significant coronary artery stenoses in autopsy series in children and young adults (Joshi et al, *Pediatr Pathol*, 1987; Paton et

al, *Res Virol*, 1993). Despite mounting evidence, however, there are no definitive data indicating that CAD is accelerated in the setting of treated or untreated HIV infection (compared to a matched HIV-seronegative adult population).

CAD Risk Factors in HIV-Infected Patients

Antiretroviral therapy has been associated with a number of metabolic abnormalities known to increase cardiovascular risk in the general population. Among these are increased total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels. Of note, the nonnucleoside reverse transcriptase inhibitor (NNRTI) efavirenz has been associated with an increase in total cholesterol level that includes a sizable increase in HDL cholesterol; increased HDL cholesterol is protective against CAD. Similarly, recent data from the Atlantic study (Van der Valk et al, 8th CROI, 2001) indicate that patients receiving nevirapine/didanosine/lamivudine exhibited a 33% increase in HDL cholesterol level, an increase of a mag-

nitude rivaling the best increases observed with lipid-modifying treatment with niacin. Insulin resistance is observed with protease inhibitor therapy, although frank diabetes is uncommon. Truncal/visceral adiposity has been epidemiologically associated with protease inhibitor-based therapy.

A recent report has indicated an association of protease inhibitor therapy with hypertension. In a retrospective review of patients presented by Hewitt and colleagues (mean age, 37 to 40 years, approximately 40% being African-American) who had no history of hypertension and had received no prior protease inhibitor therapy with the exception of hard-gel capsule saquinavir, new-onset hypertension was detected in 22% of 178 patients beginning indinavir treatment, 9% of 164 beginning nelfinavir treatment, and 7% of 104 receiving non-protease inhibitor-containing therapy (8th CROI, 2001). Kaplan-Meier analysis, correcting for time on therapy, indicated that more than 50% of indinavir recipients would develop hypertension over 600 days of exposure, compared with approximately 35% of nelfinavir recipients and 35% of

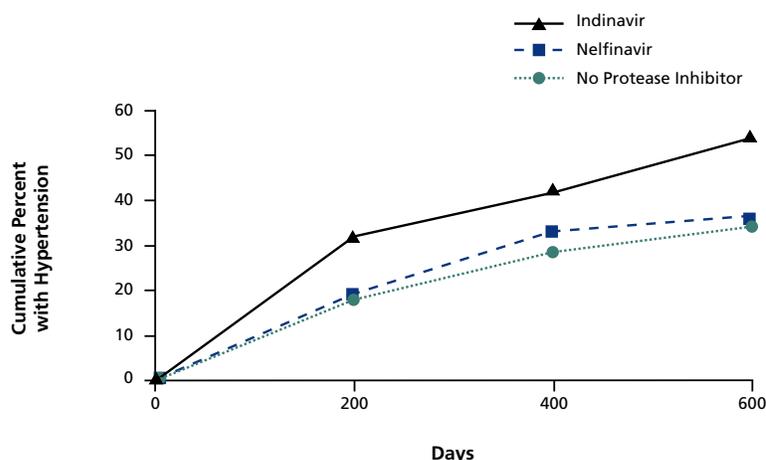


Figure 1. Kaplan-Meier plot of cumulative incidence of new-onset hypertension after start of treatment with indinavir, nelfinavir, or a non-protease inhibitor-containing regimen. Adapted with permission from Hewitt et al, 8th CROI, 2001.

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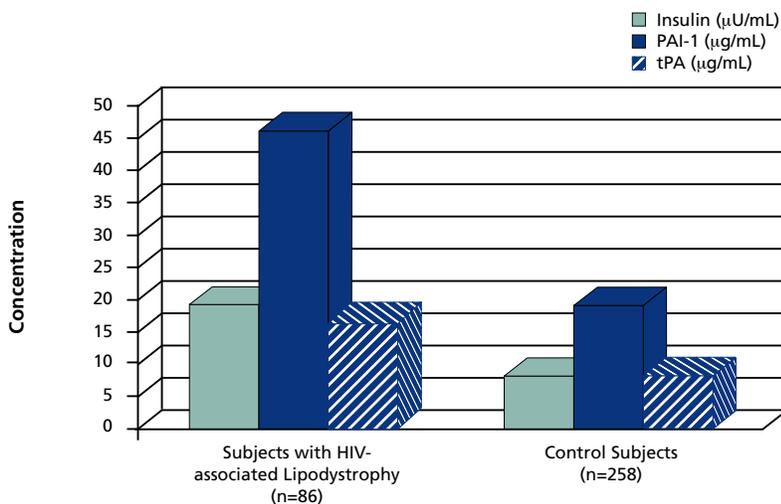


Figure 2. Comparison of insulin, plasminogen activator inhibitor-1 (PAI-1), and tissue plasminogen activator (tPA) concentrations in patients with HIV-associated lipodystrophy and control subjects without HIV infection. Adapted with permission from Hadigan et al, *J Clin Endocrinol Metab*, 2001.

recipients of non-protease inhibitor regimens (Figure 1). Although generalization from these data should be tempered by recognition that accurate blood pressure data are difficult to obtain and that the 2 groups of protease inhibitor recipients had lower CD4+ cell counts and higher viral loads at the start of treatment, the high frequency of hypertension observed in the indinavir recipients is a cause for concern.

Another recent report has indicated abnormal levels of regulators of fibrinolysis in patients with lipodystrophy. As shown in Figure 2, 86 patients with self-reported HIV-associated lipodystrophy exhibited increased levels of fasting insulin, tissue plasminogen activator, and plasminogen activator inhibitor-1 compared with 258 individuals from the Framingham Offspring Cohort matched for body mass index, age (± 5 years), and gender (Hadigan et al, *J Clin Endocrinol Metab*, 2001). The association between insulin resistance and levels of these fibrinolysis markers in the general population is well-described, and epidemiologic data suggest that elevations in these markers are associated with increased cardiac event rates in patients with documented CAD.

It should be noted that there is the potential for other risk factors not directly associated with HIV disease or antiretroviral therapy to have a high

prevalence in HIV-infected individuals. For example, Bowers and colleagues (3rd Int Conf Nutr HIV Infect, 1999) found that 70% of 102 patients assessed at a Veterans Administration HIV clinic were cigarette smokers, a proportion that is markedly greater than that in the general population. Of interest with regard to other risk factors is a recent report from Thiebaut and colleagues (8th CROI, 2001) suggesting absence of association between cytomegalovirus

serologic or disease status and carotid intimal-medial thickness as a marker for coronary atherosclerosis.

A primary concern regarding the CAD risk factors observed in HIV-infected patients is the resemblance of the complex of findings in some, particularly those with lipodystrophy, to the metabolic or insulin resistance syndrome associated with high risk for diabetes and CAD in the general population. The metabolic syndrome is characterized by dyslipidemia (increased triglyceride levels, small, dense LDL, and decreased HDL levels), insulin resistance, obesity (body mass index >25 kg/m², waist:hip ratio >0.85 , or waist circumference >100 cm), and hypertension. Definitions of the metabolic syndrome frequently include the presence of a procoagulant state.

Incidence of Ischemic Cardiovascular Events

A number of studies have sought to determine whether rates of CAD clinical events are increased in HIV-infected patients. In an analysis of data from phase 3 clinical trials of indinavir, nelfinavir, ritonavir, and saquinavir, the rate of myocardial infarction over a mean of 1 year of follow-up among 7668 patients randomized to protease inhibitor plus nucleoside reverse transcriptase

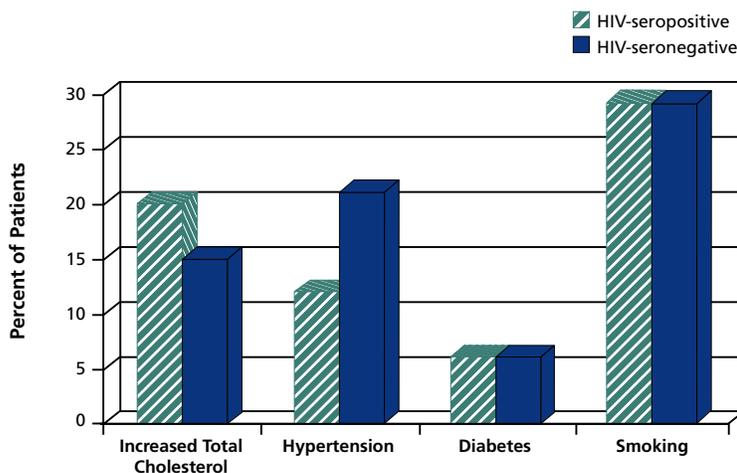


Figure 3. Proportion of 264 HIV-infected patients and 264 noninfected control subjects with increased total cholesterol, hypertension, or diabetes, or who smoked cigarettes (smoking). Adapted with permission from Klein et al, 8th CROI, 2001.

inhibitor (nRTI) therapy was found not to differ significantly from the rate among 3318 patients randomized to dual nRTIs alone (mean age of patients, 37 years), with rates being similar to those in population-based epidemiologic studies (Coplan et al, 7th CROI, 2000).

Klein and colleagues (8th CROI, 2001) recently updated findings from the Kaiser Permanente data set on hospitalization rates for coronary heart disease among HIV-infected patients stratified by protease inhibitor use and age- and gender-matched patients not known to be HIV-infected. The analysis included data only on men, since no cardiovascular events had occurred in women. Among 4541 HIV-infected men with a median follow-up time of 4.3 years (total, 14,703 patient-years), 53 hospitalizations for coronary heart disease events had occurred, yielding an age-adjusted event rate of 5.5 per 1000 population that was 60% greater than the 3.4 per 1000 population rate observed in patients without HIV infection. No difference in event rate was observed between protease inhibitor and non-protease inhibitor patient groups.

To determine the potential influence of known risk factors on this difference in event rate, risk factor data provided by a survey in the Kaiser Permanente population were compared between 264 HIV-infected patients and 264 patients without HIV infection. As shown in Figure 3, the frequency of increased cholesterol level was slightly higher in the HIV-infected patients, whereas the frequency of hypertension was somewhat lower and the frequencies of both diabetes and cigarette smoking were equivalent. These findings suggested that the increase in coronary heart disease hospitalizations among the HIV-infected patients was not due to the presence of such traditional risk factors.

In a smaller retrospective review among 951 patients receiving antiretroviral therapy without protease inhibitors between 1990 and 1998 and 383 receiving protease inhibitor-including therapy between 1995 and 1998, 5 cases of myocardial infarction occurred in the protease inhibitor group over an average of 1.5 years of follow-up and 3 occurred in the non-protease inhibitor group over 1.2 years of follow-up (Jutte et al, AIDS, 1999). Although the number of total

events was thus quite small, the risk of myocardial infarction was calculated to be increased by 5-fold in the protease inhibitor group. The incidence of 1.06 per 100 patient-years of observation (95% confidence interval [CI], 0.42-2.24) in the protease inhibitor group was significantly greater than the incidence of 0.21 per 100-patient-years (95% CI, 0.06-0.54) in the non-protease inhibitor group ($P = .025$).

In an analysis of the incidence of myocardial infarction by duration of protease inhibitor use in multiple hospitals in France through 1999, Mary-Krause and colleagues identified 54 cases of myocardial infarction in 36,907 patient-years of follow-up (8th CROI, 2001). The myocardial infarction rates increased with increasing duration of protease inhibitor exposure; although the rate decreased after 36 months, this decrease presumably is an artifact of the small sample size with exposure of such duration. Use of an age-adjusted standardized morbidity ratio showed that the rate of myocardial infarction in the patients with longer duration of protease inhibitor use was significantly greater than the rate of myocardial infarction in the general population as derived from epidemiologic data.

Although these analyses on balance indicate increased risk for cardiovascular events among patients receiving antiretroviral therapy, they are limited in important respects, including the generally short duration of follow-up and the small numbers of events observed in the studies. In addition, there is potential for biased ascertainment in the studies, with events in protease inhibitor-receiving patients being more frequently reported due to heightened awareness of the potential association of such treatment with CAD risk. Moreover, these studies generally have included no adjustments for CAD risk factors or stage of HIV disease. Since some patients included in these analyses may have been more likely to have been prescribed protease inhibitor treatment by virtue of having advanced HIV disease, the current data could mask an effect of HIV disease stage on CAD risk. It is worth noting that studies utilizing such noninvasive measures of atherosclerosis as electron beam computed tomography, carotid intimal-

medial thickness, and brachial artery reactivity have yielded conflicting results with regard to relative risk of disease in HIV-infected individuals, with some data indicating that smoking is a better predictor of abnormalities than protease inhibitor use or HIV infection status.

CAD Risk Assessment and Risk Management

With some caveats, it appears to be appropriate to assess HIV-infected individuals for CAD risk and to manage those with risk factors in a manner similar to that employed with individuals from the general population. The potential presence of risk factors should be taken into account in history taking and physical examination. In terms of specific laboratory tests, routine measurement of fasting lipid profiles can be recommended. Although there has been some advocacy for assessment of insulin levels or performance of oral glucose tolerance tests, in Dr Glesby's opinion, adoption of such testing on a routine basis may be premature given the absence of knowledge regarding how best to manage abnormalities in HIV-infected patients in order to reduce CAD risk.

With regard to overall risk assessment, American Heart Association guidelines (Grundy et al, *Circulation*, 1999) assign risk based on standard risk factors derived from the Framingham cohort study, recommending encouragement of a healthy lifestyle in individuals at low risk of coronary heart disease, aggressive risk reduction in those at high risk, and consideration of further risk stratification (eg, through noninvasive assessment of myocardial ischemia or coronary atherosclerotic burden) in those at intermediate risk. The recent guidelines of the National Cholesterol Education Program Adult Treatment Panel III (JAMA, 2001) use a similar approach of risk stratification using data derived from the Framingham study for patients in certain risk categories.

Henry and colleagues (8th CROI, 2001) performed risk assessment in a group of 100 patients randomly selected from the population of the AIDS Clinical Trials Group (ACTG) 372 study who had

achieved viral suppression on zidovudine/lamivudine/indinavir with or without abacavir and had a median duration of indinavir treatment of 42 months. Dyslipidemia and insulin resistance were common in the population, with 39% having total cholesterol levels above 200 mg/dL, 24% having LDL cholesterol levels above 160 mg/dL, 12% having triglyceride levels above 400 mg/dL, and 56% having insulin resistance by homeostatic model assessment. With use of a Framingham risk estimate instrument (see Grundy et al, *Circulation*, 1999) that determines absolute 10-year risk for coronary heart disease events based on risk points assigned for age, gender, total cholesterol level, HDL cholesterol level, systolic blood pressure, and presence or absence of diabetes or smoking, the group had an average score (4.33) that indicated moderately increased risk compared with individuals of the same age without any of the risk factors.

With regard to the use of such an instrument for risk assessment, however, it needs to be remembered that absolute risk in the Framingham population, which largely includes whites of European descent, may differ from that in other populations for any given set of risk factors. Further, the level of risk reflected in the algorithm is averaged risk, and much variability exists with regard to individual risk. In addition, the duration of dyslipidemia may be important to coronary heart disease risk, with risk in a patient who has had elevated lipid levels for many years potentially differing from that in an individual who had normal lipid levels until recently beginning potent antiretroviral therapy. It is also the case that risk might be modified in HIV-infected individuals by the presence of such potential risk factors as visceral fat, coagulability/fibrinolysis abnormalities, and insulin resistance.

As in the general population, the foundation of risk management in HIV-infected patients includes diet and exercise, smoking cessation, and treatment of hypertension. With regard to the latter, there are studies in development to evaluate potential pharmacokinetic interactions between specific antiretroviral drugs and antihypertensive agents, with there having been some concern

Table 1. National Cholesterol Education Program Adult Treatment Panel III Guidelines for Intervention Based on Low-Density Lipoprotein Cholesterol

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes† (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD or CHD risk equivalents* (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)
2+ risk factors† (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0-1 risk factor	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

*Diabetes is considered a CHD risk equivalent.

†Risk factors: (1) cigarette smoking, (2) hypertension (blood pressure ≥140/90 mm Hg or on antihypertensive medication), (3) low HDL cholesterol (<40 mg/dL), (4) family history of premature CHD (ie, CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years), and (5) age (men ≥45 years; women ≥55 years). Subtract 1 risk factor if HDL cholesterol ≥60 mg/dL.

‡Therapeutic lifestyle changes refer to a risk reduction approach involving (1) reduced intakes of saturated fats and cholesterol, (2) options for enhancing LDL reduction such as plant stanols/sterols and increased soluble fiber, (3) weight reduction, and (4) increased physical activity.

CHD indicates coronary heart disease; LDL indicates low-density lipoprotein; HDL indicates high-density lipoprotein. Adapted from National Cholesterol Education Program, *JAMA*, 2001.

over interactions between protease inhibitors and calcium channel blockers. Treatment of dyslipidemia can be performed according to National Cholesterol Education Program guidelines or the ACTG Cardiovascular Disease Focus Group guidelines (Dubé et al, *Clin Infect Dis*, 2000). Studies are ongoing to determine the effects of treatment with thiazolidinediones and metformin on insulin resistance. Studies are also ongoing to identify treatments for lipodystrophy, including studies with recombinant human growth hormone. However, the effects of even such standard treatment as lipid-lowering therapy on risk in HIV-infected patients remains unclear, since risk in these patients has not been adequately defined.

With regard to treatment of dyslipidemia, the National Cholesterol Education Program Adult Treatment Panel guidelines identify LDL cholesterol levels at which drug treatment should be initiated and target LDL

cholesterol levels according to degree of risk in primary and secondary prevention populations (Table 1). In the latest version of these guidelines, subjects whose 10-year risk of a coronary event exceeds 20% are managed the same way as those with known coronary disease. People with diabetes automatically fall into this high-risk category; for nondiabetic subjects with 2 or more risk factors, 10-year risk should be calculated using the Framingham instrument to guide management.

A small number of uncontrolled studies in small groups of HIV-infected patients with dyslipidemia have shown the expected effects in cholesterol and triglyceride level reductions from lipid-lowering treatment with atorvastatin, gemfibrozil, and pravastatin (Henry et al, *Lancet*, 1998; Hewitt et al, *AIDS*, 1999; Baldini et al, *AIDS*, 2000).

Thus far, reports of randomized, controlled studies are limited to one study of 31 subjects showing a greater

decrease in total cholesterol level and increase in HDL cholesterol level with pravastatin compared with dietary advice (Moyle et al, 40th ICAAC, 2000) and one study demonstrating a mean decrease in triglyceride level of 116 mg/dL with gemfibrozil treatment in a 16-week placebo-controlled trial in 37 patients (Miller et al, 8th CROI, 2001). Although the decrease with gemfibrozil in the latter study was statistically significant compared with placebo, triglyceride levels in gemfibrozil patients were not brought to normal levels. ACTG study A5087 currently is comparing open-label treatment with micronized fenofibrate (200 mg qd) and pravastatin (40 mg qd) for up to 48 weeks in patients with fasting LDL cholesterol level at or above 130 mg/dL and triglyceride value of 200 mg/dL or greater despite diet and exercise, with combined therapy being instituted at week 16 for inadequate lipid-lowering response at week 12. The monotherapy arms were recently closed because of failure to meet predefined criteria for successful therapy. Dual therapy is still being evaluated.

Preliminary treatment guidelines of the ACTG Cardiovascular Disease Focus Group recommend statin treatment as first choice and fibrate treatment as second choice in patients with isolated elevation in LDL cholesterol level; a fibrate or statin as first choice and combination fibrate/statin treatment as second-line therapy in combined hyperlipidemia; and fibrate treatment as first choice and statin treatment as second choice in patients with isolated hypertriglyceridemia. Although pharmacokinetic interactions between antiretroviral agents and lipid-lowering drugs have yet to be fully investigated, there is clear potential for interactions with statin drugs, since many of these are metabolized via the cytochrome P450 system. ACTG study A5047 in healthy volunteers has demonstrated interactions between ritonavir/saquinavir and statins. In this study, atorvastatin acid levels were increased by 343% and total active atorvastatin levels were increased by 74%, simvastatin acid levels were increased by 2676%, and pravastatin levels were decreased by 47%, in the presence of ritonavir/saquinavir (Fichtenbaum et al, 7th CROI, 2000). It was thus suggested that atorvastatin could be used starting

at a low dose (eg, 10 mg daily), that simvastatin should be avoided, and that pravastatin is probably safe for use. Rhabdomyolysis has been reported in a few patients receiving statins while on protease inhibitor-containing regimens.

A number of studies have assessed the effects of switching from protease inhibitors to other agents on lipid levels and insulin resistance (Table 2). In general, data from these studies indicate that lipid profiles are improved by switching from a protease inhibitor to an NNRTI or abacavir. With regard to potential treatments for other risk factors, a small placebo-controlled study has shown that metformin treatment produces a significant reduction in markers of impaired fibrinolysis in HIV-infected patients (Hadigan et al, *J Clin Endocrinol Metab*, 2001). After 12 weeks of treatment, plasminogen activator inhibitor-1 levels had been reduced from baseline by a mean of 16% ($P = .02$) and tissue plasminogen activator levels had been reduced by a mean of 11% ($P = .03$) in metformin recipients, with levels of both increasing somewhat in the placebo patients.

Less attention has been paid to lifestyle modifications, such as smoking cessation. For many patients, smoking undoubtedly confers greater risk than lipid abnormalities. Unfortunately, no data exist on smoking cessation in this patient population (Niaura et al, *Clin Infect Dis*, 2001).

Summary

The metabolic derangements observed in HIV-infected patients, whether they are associated with antiretroviral treatment or not, likely place many at increased long-term risk of accelerated atherosclerosis. This risk may be particularly enhanced in patients who have body fat distribution abnormalities. Although definitive data on risk of CAD in the HIV-infected population are lacking, the preliminary data on prevalence of CAD and incidence of clinical ischemic events do provide cause for concern. Thus, risk stratification and reduction of modifiable risk factors are indicated for HIV-infected patients.

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Table 2. General Results of Selected Antiretroviral “Switch” Studies

Initial Drug	Replacement Drug	Total Cholesterol	Triglyceride Levels	Insulin Resistance
Protease inhibitor (Gharakharian 2000, Lafon 2000, Martinez 2000, Viciano 2000)	Efavirenz	Little or no change	Variable effects	Decrease or no change
Protease inhibitor (Barreiro 2000, Negredo 2000, Raffi 2000, Ruiz 2000, Tebas 2000)	Nevirapine	Decrease or no change	Decrease or no change	Reversal or no change
Protease inhibitor (Opravil 2000, Walli 2001)	Abacavir	Decrease	Decrease	Reversal
Stavudine (Saint-Marc 1999)	Zidovudine	No change	Decrease	No change or decrease in protease inhibitor-experienced patients

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Guidelines for the Assessment and Management of Metabolic Complications

The International AIDS Society–USA has convened a panel of 12 experts to develop guidelines for the assessment and management of metabolic complications in HIV infection and antiretroviral therapy, including glucose abnormalities and insulin resis-

tance, lipid abnormalities, body fat distribution changes, lactic acidemia, and bone disease. Chaired by Morris Schambelan, MD, and Constance A. Benson, MD, the panel will submit its report for publication shortly.

Telling Stories

Mary Fisher

At the International AIDS Society–USA course in New York in March, Mary Fisher reminded us of the importance of “telling stories” by and to the community of people affected by HIV and AIDS. The transcript of her speech is reprinted below. A community, she pointed out, is a group of people bound by a common story. A community weakens without the “glue” of shared stories. With the observance this June of 20 years since the first reported AIDS cases, and as many health care practitioners and patients enter their third decade of life and work with HIV, we thought it appropriate to begin sharing common experiences of the epidemic in Topics in HIV Medicine, through a new feature called “Telling Stories.” Selected stories from those involved in HIV and AIDS care will be published here periodically.

Thank you very much. It’s a joy to be back with you, and to be so warmly welcomed.

I was honored to address the International AIDS Society–USA in May 2000 at your gathering in Washington, DC. At that time Bill Clinton was still in the White House, we hadn’t yet learned to spell “chads”—and we still thought of NIH [National Institutes of Health] as the challenge, and Wall Street as our friend. What a difference a year makes!

Being re-invited gives me an opportunity to correct one mistake I made last year. I did not tell any stories. I want to correct that oversight, beginning right now—and the first story is really a reward for those of you who chose to stay to the end of today’s session.

During Bill Clinton’s last run for the presidency—1996—I was invited to speak at an AIDS-related event in Little Rock, Arkansas. It was an awards night for regional folk who’d made significant contributions to the fight against HIV. The room was packed with social workers, people with AIDS, family members, religious leaders, a few politicians and journalists—in other words, the room was packed with Democrats. Out of deference to me, every speaker had been very discreet never to mention politics or Republicans, until the community awards were being handed out, and the last recipient wanted to talk.

She was a wonderful, elderly public health nurse: bright, quick, tiny, 77 years old, and feisty. And you could hear every politically correct person in that room stop breathing when she reached up, grabbed the microphone and said, “I’ve had it with them dumb Republicans.”

Mary Fisher is a mother, author, and AIDS activist. She created the former Family AIDS Network, which is now the Mary Fisher CARE Fund of the University of Alabama at Birmingham. This not-for-profit fund sponsors long-term outcomes research that will impact HIV/AIDS care and public policy. Ms Fisher is a special friend of the International AIDS Society–USA and has contributed to the organization on many levels, not the least of which being to inspire us to think about new ways to serve our audience in their work in HIV/AIDS research and clinical care.

“For 15 years,” she said, “I’ve talked to them dumb Republicans. Over and over, I’ve explained there ain’t but 3 ways you can get AIDS: swap needles or blood, have sex, or get born with it. And, for 15 years them dumb Republicans been askin’, ‘But can’t you get it from mosquitoes?’”

She paused for a moment, and then she said: “I’m tellin’ y’all tonight that, from now on, I’m gonna tell ‘em, ‘Yep, you can get it from mosquitoes—but only in 3 states: Florida, Louisiana, and Arkansas. Cause them’s the only places mosquitoes grow so big Republicans can have sex with ‘em.”

Of all the stories I’ve collected while traveling the road to AIDS, this is probably my favorite. I’ve told it as truthfully as it happened—because you can’t improve on the reality of it.

Stories are important, also to you and me. When I was first diagnosed with HIV in 1991 and when many of you first joined the fight, the AIDS community had its own story. It was a story of mysterious reports and sudden wasting, of an unnoticed community of people with hemophilia whose lives were suddenly being cut short, and a previously hidden gay community whose fabric and texture was suddenly, brutally, being exposed by AIDS. Headlines told stories of families making 3 discoveries simultaneously: their brothers were gay, their brothers were sick, and their brothers were dying.

Part of the story was told quietly by the Names Project AIDS Memorial Quilt founded by Cleve Jones and friends. It was told in the ritual unfolding of panels in temple basements and college gyms across the nation. Walking the edge of the quilt, the mother—who’d insisted to her bridge club that her son had died of cancer—found courage to tell the truth, to tell his story, to crochet a memory into a panel the size his coffin had been. How many stories have you and I heard? How many times did the whisper of unfolding panels make us shiver, and tear-up, and grab hold of the hand next to ours? In their refusal to let us go anonymously to the grave, Cleve and company assured a memory of the stories.

Part of the story was blared into cameras and screamed into the night by Larry Kramer and his ACT UP warriors. They loaded press releases and aimed them at *The New York Times*; they loaded condoms and threw them at the president’s motorcade. In their rage, they told another story about AIDS: about those who believed gay men deserved to waste away, about those in power who preferred prejudice to compassion and cowardice to honor. So important was their story, and so powerful their fury, that I dreaded them when I spoke to the 1992 Republican convention. I feared they would say I had sold out: that I didn’t understand because I was a woman, not a gay man; that I didn’t belong with them, because I’d come from a family with means whose father spoke to presidents.

Both the quilt and ACT UP are, today, mostly memories. The past presidential election was the first in the history of AIDS in which the quilt, in all its grief and glory, was not lain across

Washington’s Mall. ACT UP is still alive, but its founder is fighting to live, not living to fight.

The image of the quilt and the echo of ACT UP remind us that, once upon a time, the American AIDS community had a common story. All of us—gay or straight—had tasted the stigma championed by select members of Congress and leaders in a series of administrations. The story of being disenfranchised by a virus was our story; it belonged to all of us. It helped make us a community.

All of us—male or female—had known the rage that built within us, the grim, unbending suspicion that if AIDS was a death sentence, people in power did not mind. We rallied and we protested. Tom Hanks’ *Philadelphia* was our story, our fight for dignity. It gave us a sense of community.

All of us—physicians and patients, Democrats and (God knows) Republicans—soon learned that dealing with AIDS was different than dealing with heart disease and cancer. We knew it when our families wished we’d come down with a different disease or our in-laws wished we’d chosen a different clinical specialty. The story of AIDS was seen as a dirty story, something not to be mentioned around the children. At the same time, it was our story: it was what bonded us. The sheer magnitude of AIDS shrunk the importance of gender and race, of politics and degrees. Our common affinity with AIDS made us citizens of a single community.

The hardest thing to find in the AIDS epidemic today—whether you are a physician or a policy buff, an activist or a journalist—is

an American AIDS community. We can use the phrase, “American AIDS community,” but it has no substance. We are not one anymore, no matter how a virus may be touching each of us. We are divided into silos of interest and self-interest, a few advocates and many drug manufacturers, researchers, and physicians. We are divided by economics and geography and ethnicity. We are seen less as a national community than as a government category. We are not a political force. We are, in fact, just barely a political issue.

Communities have leaders. Their names fall naturally from our lips. I mean no disrespect to the extraordinary women and men whose pictures decorate *Time* magazine and whose stories are well known within the world of infectious diseases. But when I think of an AIDS community, it feels as though the leaders have, mostly, died. When I wander through my art studio, and see works I finished in 1993, ‘94, ‘95, I remember again that Elizabeth is gone, Arthur is gone, Paul is gone. They’re all gone. It’s hard to lead when you’re dead.

Communities have rituals by which we remember our common tradition. That was the role of the quilt, constantly growing, constantly reporting its own growth. It told the AIDS community’s story as a growing story of a swelling epidemic. The community’s rituals have mostly faded now. We folded them up with the quilt in the fall of ‘96. We put them, mostly, away.

Communities have symbols, which was the importance of the red ribbon before other diseases—easier to champion, more popular at home—changed the color and the cause.

This is not, despite how it may sound to you at the moment, a wishing for “good old days” when people with AIDS were dying left and right. I’m not wistful for the agony that came along with those years, or naive about the vast improvements that have been made in the treatment of AIDS. I am grateful for the advances. But I am haunted, and some days distraught, at our collective and profound loss of community.

And it is not only an American community for which I long; it is a global AIDS community. I’ve stood in the African dust with sisters whose children are dying. I’ve looked across acres of orphans while holding the hands of my own sons. This is not an academic exercise for me, or an emotional appeal for Americanism.

Most Americans believe there is no need to have an AIDS community because they believe AIDS has a cure, just like diabetes. They believe AIDS is an African problem because people in Africa can’t afford to be cured; if only those Africans had more cash, they too would be fine. When I try to explain that AIDS is not cured, most Americans believe I’m merely whining. There’s a cure—they’re sure of it; they know it. African American youth believe it because of Magic Johnson. Other folk believe it because what else would a “manageable disease” be, if not “cured”?

So, yesterday, many of us were asked to mount pressure on the administration to restore funding for AIDS-related programs that appear to have disappeared in President Bush’s budget for next year. The Minority HIV/AIDS

Initiative, some CDC [Centers for Disease Control and Prevention] prevention programs, and some HRSA [Health Resources and Services Administration] care programs all look to be emptied or gone. Congresswoman Nancy Pelosi, a Democrat from California, and Congressman John Shimkus, a Republican from Illinois, have drafted a letter calling for restoration of these funds. We need to drum up support.

The challenge we face is largely one of communication. These good congress people are going to cite statistics of infections. They’ll tell the president that the CDC reports 900,000 Americans with HIV. And in the backrooms and corridors where power brokers do their work; in the press rooms and editorial boards where the American mind is shaped; in the lobbying firms who want these monies for their clients—they know, they absolutely know, that there is no clamoring, protesting, voting American AIDS community, because AIDS in America is cured.

Which brings me back to the matter of stories. A community is, in many respects, a group of people bound together by a common story. What made Israel “Israel” is a common story brought down from Fathers Abraham, Isaac, and Jacob. What makes the Ute people or the Navajo people a “people” is not simply common DNA, but common stories. What sets the DiAngelo family apart from the Hernandez family and the Jones family is their uniquely woven set of stories called “family tradition.” It’s stories that tell us who we are, where we belong, where we find our place among others. The absence of such stories means we are, in some profound ways, orphans—which is why

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so many of those with AIDS today have no context, no support systems, no advocates. They are without the community that defines us and cares for us and makes us, somewhere between cradle and grave, human.

Stories are our way of making sense out of what cannot be explained, our way of making enduring what could otherwise not be endured. Paul Rudnick, the wonderful writer, once explained why gay men have written comedies about AIDS. "Only money, rage, and science can conquer AIDS," he said. "But only laughter can make the nightmare bearable."

One of the reasons I love telling the story of that sainted public health nurse and her Republican-loving mosquitoes is because it says something of the AIDS community. If you knew nothing of AIDS political history, it wouldn't be funny. But it plays on our American story, and our sense of the impossible. It's like Jewish humor or Italian humor; it's "inside humor," an AIDS community joke. Besides, it makes us laugh—which makes the nightmare bearable.

So here's my call to you today. I want you to start gathering, and shaping, and telling, and publishing stories. That's right: stories. We need to humanize AIDS again, taking it out of the dusty realm of statistics and projections. We need to reattach AIDS to something human, something that slashes into a family and matters to a congregation. Both the media and the politicians know the numbers; what they don't know is that the numbers matter. They don't think of a half-million deaths as a half-million stories; they think of them as one story told a half-million times.

When a congresswoman needs to move a piece of legislation, she puts out a call to her district for stories. Those stories become human when they appear in legislative rooms as witnesses, and in press stories as examples. When a president wants to advance a new policy, he looks for a family to plant in the House Gallery for his speech. He looks for people who are the story. These people know that, when thinking of the Holocaust, the number "6 million" has no meaning until you attach it to Anne Frank's story.

The fact that we have let the American AIDS community grow mute and scattered; the fact that our numbers are being reported but our story isn't being told—it is, if you'll forgive me for putting it this way, what is killing us.

We have a new administration forming in Washington, DC. We have hints that Colin Powell may regard the international AIDS crisis as a profound and moral responsibility that rests not solely, but seriously, with him. The secretary of state knows the numbers. But what he may need, either to bolster his own support or, more likely, to enable him to generate support among others, is stories: stories that show Americans care about AIDS, stories that rise from families who have lost loved ones and can identify with the African mother staring at her soon-to-be orphans. To mount an American response, he needs to know that there is an American community of interest—not just pockets of professional self-interest—in AIDS. (What do you think

America's policy toward Israel would have been for the past 50 years if there were no American Jewish community?)

Governor Thompson is now Secretary Thompson. His record, and his attitude, could give us reason for some hope. But what he experiences as "AIDS" is not—not in his office, not on his timeline—so much a human crisis as a budget dilemma. If all he hears is numbers and statistics from us—if we leave him to work in a nation that believes AIDS is cured—he'll have neither voices nor witnesses nor probably motivation with which to fight budget challenges and bureaucratic chaos. If he is to advance our cause, then he needs witnesses. And we must tell him the truth.

I understand that most of you are scientists, not street-level advocates. I thank God for you. Don't for a moment believe I think science does not matter. I have 2 children at home who love me. Science matters to our family. It matters very much.

But so do stories. Because it is not science that teaches us who we are, or what we are to do with our lives, or why we matter, or how we will be loved. We don't, and neither do you. You discover who you are when, after an impossibly long day of work with paper and people, you finally give up and go to bed. And, somewhere in the night, you hear the voice of someone with whom you once knew romance. If she says, "I love you," you drift off to sleep. And if she says, "I can't go on like this . . .," you stay awake. In the end, you see, it isn't our statistics that define us; it's our story.

If you want to support one another as scientists, physicians, caregivers, you need time to tell each other stories, not just statistics. You need inside humor. You need to be not only members of an academy but members of a community. If I had a wish to waste, it would be this: I'd love to get you to tell stories to each other and to me: the ridiculous and the sublime, the funny and the sad. Stories lift us up, inspire us, shake us from the professionalism and soberness that tend to associate with events such as this. They give us hope.

I am a great fan of the International AIDS Society–USA. I count a number of you here today as my closest friends and advisors. For example, there is Dr Michael Saag: my professional colleague, my personal physician, and my cousin. If he doesn't like what I say in these settings, he still tells my mother.

I know the importance of research and discovery to Michael. I know why the numbers matter to him. But it isn't statistics that will enable Michael, or any of you, to re-engage and build an AIDS community, it's stories. Let me give you an example on my way out.

This story is taken from *I'll Not Go Quietly*, a book we published in 1995.

Billy Cox came out of his hospital bed in Birmingham, Alabama, to bring me a hug in Montgomery.

I'd first met him a year earlier at the University of Alabama at Birmingham where I was visiting Michael Saag . . . Michael wanted me to meet Billy, to see his spunk and spirit. "Billy's the boxer in the

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ring,” Michael once observed. “The doctors and nurses and medical staff, we’re just the trainers in his corner. His friends and family are his fans, cheering him on.”

Now, a year later, I’d come to Montgomery to speak... But what I said there was not as eloquent as the events that soon played out in the life of Boxer Billy and Cousin Michael.

Six weeks after he’d brought his hug to Montgomery—7 years, 4 months, and 3 days after testing positive for the AIDS virus—Billy Cox died. November 23, 1994.

On Billy’s last day, Michael Saag was leaving town for a few days and stopped in just to say good-bye. When he heard Billy’s labored breathing, he called the family together and told them the end was near. And then—as nurses and old friends and Billy’s family crowded into the room, forming a remarkable community bound only by love for the boxer—Michael rested his head on Billy’s chest and, unashamed, before the crowd, sobbed, “I’m sorry, I’m sorry.”

Science has limits. Even community has bounds. But no one will ever know what love might do.

A community is defined by its stories: stories of victory and loss, of heroes and scapegoats, of tragedy and triumph. For the American AIDS community to become a community again, we must find ways to tell the stories again, to let others know that after Billy Cox came others, each with a name, each with a purpose, each with a life.

In my own story, you are the heroes. You are the ones whose stories matter most, whose values need to shape policies, whose passions need to find headlines. In my story, you are the ones who will be first to hear the words of the ancient rabbi: “Grace to you, and peace.”

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¹International 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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Hilton New York, New York, New York

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Current Issues in the Management of HIV

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