Is That “One Pill” Treatment Enough?

A 61-year-old woman is seen to discuss antiretroviral options. She acquired HIV infection from her husband (who has since died of AIDS) in the early 1990s, if not before. In 1996, with a CD4 count of 550 cells/mm³ and a viral load of 1990s, if not before. In 1996, with a CD4 count of 550 cells/mm³ and a viral load of 43,000 copies/mL, she started 3T and 3TC. She tolerated the drugs well but experienced mild thinning of the face and extremities. She continued on the regimen until 2002, when it became clear, in retrospect, that she did not meet current criteria for starting therapy. At the time of treatment cessation, she had a viral load of 5000 copies/mL and a CD4 count of 680 cells/mm³; a resistance genotype showed the M184V mutation.

Since this patient stopped treatment, the mild thinning she experienced on therapy has improved slightly. Her viral load has consistently been between 30,000 and 100,000 copies/mL, and her CD4-cell count has declined gradually. At the present visit, her CD4 count is 290 cells/mm³, and she agrees to re-start therapy. The only medications she currently takes are hydrochlorothiazide and lisinopril for hypertension. She specifically requests the “one-pill” treatment.

Would you prescribe coformulated tenofovir/FTC/efavirenz (Atripla) for her? Why or why not? If not, what treatment would you recommend? Would you request a viral tropism test?

JOEL E. GALLANT, MD, MPH

I would not prescribe tenofovir/FTC/efavirenz for this woman, because she has documented resistance to FTC, one of the three components of the regimen. In this setting, the combination would essentially be a two-drug regimen in which both active drugs have a low genetic barrier to resistance.

Combining a ritonavir-boosted PI with tenofovir/FTC would be the easiest option, allowing her to take a once-daily regimen with a low pill burden. Although one could argue that this is still a two-drug regimen because of FTC resistance, boosted PIs are known to have higher barriers to resistance than do NNRTIs. Furthermore, although M184V is archived in this patient’s latent reservoir, FTC is likely to be active against her circulating virus. Finally, should M184V be reselected, the mutation would increase the activity of tenofovir.

In the past, when treating patients who had known 3T/FTC resistance, I often prescribed three NRTIs (tenofovir/FTC + AZT) plus either a boosted PI or efavirenz, to take advantage of M184V-induced hypersusceptibility to both tenofovir and AZT. However, I’m less inclined to use AZT now that other agents are available that are safer, more potent, and better tolerated — and it would be an especially poor choice in this patient, who already has lipoatrophy from prior use of d4T. When AZT is being used for resistance reasons, I sometimes replace it with raltegravir. For example, I would expect the combination of raltegravir plus tenofovir/ FTC/efavirenz to be effective in this patient, although it would require twice-daily dosing. Another option would be to turn the combination of tenofovir/FTC plus a boosted PI into a solid three-drug regimen by adding raltegravir, but this might be unnecessary for the reasons discussed above.

I would not order a tropism test in this patient because I have no immediate plans to treat her with maraviroc. A patient who has only the M184V mutation has many effective treatment options that don’t require extra testing. In this patient, the provider had the foresight to order a genotype before...
STOPPING TREATMENT WITH d4T AND 3TC. THE MORE COMMON CASE IS THE PATIENT WITH PRIOR USE OF NONSUPPRESSIVE DUAL-NRTI THERAPY WHO DOES NOT HAVE RESISTANCE DATA AVAILABLE. IF THAT HAD BEEN THE CASE HERE, I WOULD HAVE ASSUMED THE WORST: THAT A PATIENT TREATED FOR 6 YEARS WITH TWO NRTIS HAS NOT ONLY M184V BUT ALSO MULTIPLE THYMIDINE ANALOGUE MUTATIONS THAT COULD RESULT IN CROSS-RESISTANCE TO TENOFOVIR AND OTHER NRTIS. IN THAT CASE, I WOULD HAVE NO CONFIDENCE IN NRTIS AND WOULD CONSIDER USING A BOOSTED PI PLUS AN NNRTI, A BOOOSTED PI PLUS AN INTEGRASE INHIBITOR (RALTEGRAVIR), OR POSSIBLY A REGIMEN CONTAINING ALL THREE OF THOSE CLASSES.

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RESPONSE 2

JOSE R. ARRIBAS, MD

BEFORE MAKING ANY TREATMENT RECOMMENDATIONS, I WOULD FIRST ORDER A NEW GENOTYPIC RESISTANCE TEST TO RULE OUT RECENT SUPERINFECTION WITH RESISTANT HIV AND TO DEMONSTRATE THE LOSS OF M184V AFTER 6 YEARS OF ANTIRETROVIRAL TREATMENT INTERRUPTION. I WOULD ALSO ORDER A TROPISM TEST, WHICH I CONSIDER TO BE A ROUTINE PART OF RESISTANCE TESTING. MOST LIKELY, RESISTANCE GENOTYPING WOULD SHOW WILD-TYPE HIV, BECAUSE M184V TENDS TO DISAPPEAR WITHIN WEEKS AFTER PHARMACOLOGIC PRESSURE IS WITHDRAWN (CLIN INFECT DIS 2005; 41:236).

THE SAFEST APPROACH FOR THIS PATIENT WOULD BE TO ASSUME THAT HER HIV IS ALREADY RESISTANT TO 3TC/FTC AND MIGHT HAVE SOME HIDDEN RESISTANCE TO THYMIDINE ANALOGUES. THEORETICALLY, COFORMULATED TENFOVIR/FTC/EFAVIRENZ HAS ONLY A VERY SMALL CHANCE OF BEING EFFECTIVE AND SO SHOULD NOT BE RECOMMENDED. AS AN ALTERNATIVE, I WOULD USE A BOOSTED PI PLUS A SECOND FULLY ACTIVE DRUG, SUCH AS EFAVIRENZ, RALTEGRAVIR, OR MARAVIROC (IF THE VIRUS IS FOUND TO BE CCRT5 TROPIC). NO CLINICAL TRIAL DATA ARE AVAILABLE TO SUPPORT ONE OPTION VS THE OTHERS IN THE CONTEXT OF ISOLATED RESISTANCE TO 3TC/FTC. DUAL THERAPY IS VERY LIKELY TO BE ENOUGH, BUT SOME CLINICIANS WOULD STILL ADD A THIRD DRUG, SUCH AS TENOFOVIR, TO COMPLETE AN “ORTHODOX” TRIPLE-DRUG REGIMEN.

WHAT IF THE PATIENT REALLY WANTS TO TAKE TENFOVIR/FTC/EFAVIRENZ? IF GENOTYPING SHOWS WILD-TYPE HIV, AS I WOULD EXPECT, THEN WE SHOULD HAVE TIME TO TEST SUCH AN “UNORTHODOX” APPROACH, GIVEN HER LATEST CD4-CELL COUNT. EFAVIRENZ WOULD BE FULLY ACTIVE, TENOFOVR WOULD LIKELY HAVE SUBSTANTIAL ACTIVITY, AND FTC SHOULD RETAIN SOME ACTIVITY AGAINST THE MAJORITY WILD-TYPE POPULATION, AT LEAST IN THE SHORT TERM (6 MONTHS), IF REVERSION OF NEVIRAPINE MUTATIONS OCCURS (N ENGL J MED 2007; 356:135). THIS SCENARIO MIGHT SOMEWHAT RESEMBLE WHAT WE COULD EXPECT IN OUR PATIENT. WE CAN BE ALMOST SURE THAT THIS PATIENT HARBORS A MINORITY POPULATION OF VIRUSES WITH M184V THAT IS NOT GOING TO BE DETECTED BY POPULATION GENOTYPING. WILL THIS MINORITY POPULATION BE ENOUGH TO GUARANTEE FAILURE OF TENOFOVIR/FTC/EFAVIRENZ?

INTERESTINGLY, A RECENT ANALYSIS FROM THE ACTG 5095 TRIAL SHOWED THAT 29% OF PATIENTS WITHOUT VIROLOGIC FAILURE ON AZT/3TC PLUS EFAVIRENZ HAD DETECTABLE Y181C (ABSTRACT 83, 15TH RETROVIRUS CONFERENCE, 2008). COULD TREATMENT WITH TENOFOVIR/FTC/EFAVIRENZ ALSO BE SUCCESSFUL OCCASIONALLY IN PATIENTS WHO HARBOR MINORITY POPULATIONS WITH M184V?

IN SUMMARY, I WOULD EXPLAIN TO THE PATIENT THAT OTHER OPTIONS ARE PREFERABLE, BUT IF SHE IS DETERMINED TO USE TENOFIYFV/FTC/EFAVIRENZ, I DO NOT THINK WE WOULD LOSE A LOT BY TRYING. IF THE VIRUS DEVELOPS M184V AND K103N, AND THE REGIMEN SUBSEQUENTLY FAILS, WE COULD STILL DESIGN A REGIMEN THAT IS VERY LIKELY TO BE ACTIVE. BOOSTED PIS ARE AN OPTION FOR THIS PATIENT, AS IS EFAVIRENZ, WHICH IS ACTIVE IN THE PRESENCE OF K103N.

Dr. Arribas is Associate Professor of Medicine at the Autónoma University School of Medicine and an attending physician in the HIV Unit at Hospital La Paz in Madrid, Spain.

TELL US WHAT YOU WOULD DO

How would you manage this patient? Send your thoughts to arcase@mms.org, and we’ll publish a selection of your responses in an upcoming issue.
Monitoring Patients for ART Failure in Resource-Limited Settings

A computer model may provide false reassurance regarding the value of clinical observation versus laboratory monitoring.

In resource-limited settings, the value of viral loads and CD4-cell counts for monitoring the progress of HIV-infected patients before and after the initiation of antiretroviral therapy (ART) remains controversial. On the one hand, recent cost-effectiveness studies favor CD4-cell monitoring over clinical observation alone, even in some of the poorest nations (N Engl J Med 2006; 355:1141). On the other hand, current WHO guidelines recommend that clinically eligible patients receive HIV therapies, regardless of whether concomitant laboratory monitoring can be provided.

To inform this debate, investigators constructed a computer simulation model that evaluated how three different types of monitoring for antiretroviral failure might influence outcomes:

- Viral-load monitoring (failure defined as viral load >500 copies/mL or, in some analyses, as >1000 copies/mL)
- CD4-cell-count monitoring (failure defined as a drop in CD4-cell count ≥50% from peak or, in some analyses, as ≥33% in a 6-month period)
- Clinical observation (failure defined by various combinations of new WHO stage 3 and 4 events)

The model assumed that patients would receive the WHO-recommended first-line combination of d4T, 3TC, and nevirapine and that they would be switched to second-line therapy at the time of failure. Outcomes of interest included estimated survival, use of second-line regimens, emergence of resistance, costs, and cost-effectiveness.

Over a 5-year horizon, the predicted survival of HIV-infected patients receiving ART with viral-load monitoring was 85% that of persons living without HIV infection. Corresponding values were 82% with CD4-cell-count monitoring and 82% with clinical observation alone. Over a 20-year horizon, the predicted survivals were 67%, 64%, and 64%, respectively.

The model suggests that viral-load monitoring might provide false reassurance to clinicians, patients, and policy makers alike. The additional survival benefits of CD4-cell–count monitoring in this study are much smaller than those reported in prior model-based evaluations. Moreover, measures of comparative performance and value are most appropriately presented in reference to a benchmark standard. Current WHO guidance recommends the use of national income statistics for this purpose. Specifically, interventions can be considered “cost-effective” in a given country if they confer additional life-years at a cost less than three times the nation’s per capita gross domestic product. By this standard, it is not at all clear that the authors have identified either the most appropriate or the most cost-effective approach to patient monitoring. The interpretation of findings is further hindered by the authors’ failure to eliminate “weakly dominated” alternatives (i.e., strategies that cost more but deliver fewer benefits than some combination of other strategies); this basic methodological error results in a misrepresentation of the comparative attractiveness of several of the strategies under consideration.

Millions of untimely deaths will result from delays in the global scale-up of access to HIV therapies. Although laboratory monitoring at the intensity currently practiced in the U.S. and Europe is neither feasible nor cost-effective in resource-limited settings, the case for clinical observation as an acceptable substitute for all laboratory monitoring has not yet been made.

— A. David Paltiel, MBA, PhD

Dr. Paltiel is Professor of Public Health at the Yale School of Medicine.

**Comment:** This study may provide false reassurance to clinicians, patients, and policy makers alike. The additional survival benefits of CD4-cell–count monitoring in this study are much smaller than those reported in prior model-based evaluations. Moreover, measures of comparative performance and value are most appropriately presented in reference to a benchmark standard. Current WHO guidance recommends the use of national income statistics for this purpose. Specifically, interventions can be considered “cost-effective” in a given country if they confer additional life-years at a cost less than three times the nation’s per capita gross domestic product. By this standard, it is not at all clear that the authors have identified either the most appropriate or the most cost-effective approach to patient monitoring. The interpretation of findings is further hindered by the authors’ failure to eliminate “weakly dominated” alternatives (i.e., strategies that cost more but deliver fewer benefits than some combination of other strategies); this basic methodological error results in a misrepresentation of the comparative attractiveness of several of the strategies under consideration.

**Rifampin and Lopinavir/r: A Combination to Avoid**

A study of rifampin with lopinavir/r among healthy volunteers was stopped early because of nausea, vomiting, and increases in liver-enzyme levels.

Millions of people worldwide are coinfected with tuberculosis (TB) and HIV. For those who require concomitant treatment but cannot receive NNRTIs (e.g., because of intolerance or resistance), options are extremely limited. Standard-dose PIs cannot be coadministered with rifampin because plasma levels of the antiretrovirals are reduced by 70% to 90% in this setting, rendering the drug ineffective.

In this pharmacokinetic study, researchers sought to evaluate the effect of rifampin on adjusted dosages of lopinavir/ritonavir in the tablet formulation. The study design called for 40 healthy volunteers to receive rifampin alone for 5 days and then with lopinavir/r (600/150 mg twice daily or 800/200 mg twice daily) for 10 days. However, the study was aborted after only 11 people had enrolled, because of adverse events that occurred during concomitant administration of rifampin and lopinavir/r:

- Ten volunteers experienced nausea, vomiting, or both.
- Starting on day 7, all enrollees had dramatic increases in aspartate aminotransferase (AST) levels.
- AST levels in all enrollees were significantly higher than levels in control subjects.
- The authors chose not to proceed further with testing this combination of agents.

**References:**

aminotransferase (AST) and alanine aminotransferase (ALT) levels, and 10 had increases in gamma-glutamyl transferase levels. Medication was stopped in all participants by day 8; liver-enzyme levels continued to rise, peaking on days 9 through 12.

- Eight volunteers experienced grade 4 AST or ALT toxicity: four of six in the 800/200-mg lopinavir/r group and four of five in the 600/150-mg group.

Comment: The authors offer several possible explanations for the unexpectedly high rate of hepatitis in this study compared with their previous evaluation of rifampin and lopinavir/r. In that study, the capsule, rather than the tablet formulation, was used; rifampin and lopinavir/r were administered simultaneously rather than sequentially; and there was escalation of the lopinavir/r dose. However, the current study design, particularly the initiation of TB treatment before antiretroviral therapy and the absence of dose escalation, more closely mirrors the combined use of TB and antiretroviral drugs in clinical practice. The results therefore argue strongly for avoiding concomitant use of rifampin/r and rifampin until additional information is available. This is bad news indeed, as it further limits treatment options for the many TB/HIV-coinfected patients who cannot use NNRTIs. Given the dire implications of these findings, they should be confirmed by immediate review of experience in large treatment cohorts to determine whether increased hepatotoxicity with this combination has occurred in the field.

— Gerald H. Friedland, MD


Low Rate of Vertical HIV Transmission in the U.K. and Ireland

Only three cases of transmission occurred among 2117 infants whose mothers achieved undetectable viral loads in response to ART.

Successful prevention of vertical HIV transmission hinges on the mother receiving antiretroviral therapy (ART). In this study, which was previously reported at the 15th Retrovirus Conference (Abstract 653; see AIDS Clin Care Apr 2008, p. 30), researchers described the experience of more than 5000 women who received antiretrovirals during pregnancy between 2000 and 2006 in the U.K. and Ireland.

The overall rate of vertical transmission was 1.2% (61 of 5151). Rates were even lower in certain circumstances: 0.7% (17 of 2286) with combination ART and planned cesarean delivery, 0.7% (4 of 559) with combination ART and planned vaginal delivery, and 0% (0 of 464) with AZT monotherapy and planned cesarean delivery. Only three transmissions occurred (0.1%) among the 2117 infants whose mothers achieved viral loads <50 copies/mL with combination ART. In an analysis that was adjusted for viral load, mode of delivery, and sex of the infant, longer maternal exposure to combination ART was associated with a lower rate of transmission (10% reduction with each week of treatment).

Comment: These data nicely document the tremendous beneficial effect that contemporary ART use has on vertical transmission rates. Particularly noteworthy is the 0.1% rate seen among women who achieved undetectable viral loads in response to ART. For two of the three cases of transmission that occurred among these women, there was evidence of in utero infection.

NEWS IN CONTEXT

FTC + Atazanavir + ddi Deemed Inferior to AZT/3TC + Efavirenz

A once-daily initial regimen of FTC, atazanavir, and ddi is less effective at controlling HIV than is a twice-daily initial regimen of AZT/3TC + efavirenz, according to a large, international ACTG trial. The finding recently emerged during an interim review by the Data and Safety Monitoring Board and has led the study sponsor (the National Institute of Allergy and Infectious Diseases) to discontinue use of the regimen in this trial.

The ongoing phase IV trial involves 1571 HIV-infected patients in Africa, the Americas, and Asia who were randomized to one of three initial treatment regimens:

- AZT/3TC twice daily + efavirenz once daily
- FTC + atazanavir + enteric-coated ddi, all taken once daily
- FTC/tenofovir + efavirenz, all taken once daily

Study participants who were receiving FTC, atazanavir, and ddi are being advised to switch regimens in consultation with their physicians. They will continue to be followed by study investigators as planned.

Comment: These results add to a substantial body of data confirming that unboosted PIs are less effective virologically than efavirenz-containing regimens. Interestingly, one of the only studies that did not show the superiority of efavirenz was another comparison of efavirenz with unboosted atazanavir (J Acquir Immune Defic Syndr 2004; 36:1011), but the results of that study have been called into question because of the way specimens were collected for viral-load analysis.

These interim findings have little bearing on clinical practice in the U.S., where the combination of FTC, atazanavir, and ddi is rarely used and boosted-PI regimens are clearly favored. However, unboosted PIs might have had greater appeal in developing countries because the current ritonavir formulation is not heat stable, making it hard to use in areas where refrigeration is not reliably available.

The full results of ACTG 5175 await the ongoing comparison between the two efavirenz-containing arms — AZT/3TC plus efavirenz versus FTC/tenofovir plus efavirenz. — Paul E. Sax, MD

Overall mortality rates were similar across groups; after 6 months, control infants had slightly but not significantly higher mortality rates, apparently because of their higher HIV infection rates. Side effects from the drugs were rare; no information was provided about drug-resistance problems in infants who became infected despite prophylaxis.

A less successful intervention was reported from Zambia, where 958 HIV-infected women were randomized to wean infants abruptly at 4 months or to continue breast-feeding for as long as they liked. Although women in the early-wean group received intensive counseling, formula, and cereal, only 70% successfully weaned their infants by 5 months (vs. 7% in the control group). An intent-to-treat analysis showed only a slight, nonsignificant difference in HIV infection rates between the groups (21% in the early-wean group vs. 26% in controls). Mortality at 24 months was similar for uninfected children in both groups, but, among HIV-infected infants, mortality was significantly higher in the early-wean group.

Comment: These important studies are likely to affect policy — in fact, results from the Zambian study have already weakened the WHO’s previously strong recommendation to stop breast-feeding at 6 months. Still, they raise as many questions as they answer. Antiretrovirals clearly reduce transmission, but the issue of drug resistance is still unresolved, and providing antiretrovirals for the duration of breast-feeding poses a clear financial burden. Meanwhile, limiting breast-feeding could be nutritionally dangerous to sick children and unacceptable to their mothers. Editorialists point out that in this arena, scientists will have to adapt their prevention strategies to a variety of cultural, economic, and psychological factors.

— Abigail Zuger, MD


Cancer Incidence Among HIV-Infected Patients

Rates of several non-AIDS-defining cancers are higher in HIV-infected patients than in the general U.S. population.

Since the widespread introduction of potent antiretroviral therapy (ART), the burden of cancer in the HIV-infected population has shifted away from AIDS-defining malignancies (most of which are related to immunosuppression) toward more non–AIDS-defining cancers. Two recent studies described the incidence of both types of cancer among HIV-infected patients in the U.S.

In the first study, investigators reviewed data collected from 1996 through 2005 from 2566 patients in the Johns Hopkins HIV cohort. Of the 253 incident cancers identified, 55% were AIDS-defining. During the study period, the incidence of AIDS-defining cancer decreased significantly (from 12.5 to 3.5 cases per 1000 person-years), largely because of a dramatic drop in new cases of Kaposi sarcoma and non-Hodgkin lymphoma. At the same time, the incidence of non-AIDS-defining malignancies seemed to increase (from 3.9 to 7.1 cases per 1000 person-years), although the change was not statistically significant. The most common non-AIDS-defining cancers occurred more frequently in the cohort than in the general U.S. population (standardized incidence ratios, 5.5 for lung cancer, 5.1 for head and neck cancers, 16.5 for liver cancer, and 39.0 for anal cancer).

At the time of cancer diagnosis, patients with non-AIDS-defining malignancies tended to be older than those with AIDS-defining cancers; they also had higher CD4-cell counts, were less likely to have a history of opportunistic infections, and, if they were on ART, were more likely to be viremically suppressed. The two groups did not differ with respect to ART exposure, either at the time of cancer diagnosis or beforehand. Median survival time after cancer diagnosis was 315 days for patients with AIDS-defining cancer and 654 days for those with non-AIDS-defining cancer.

In the second study, investigators evaluated data collected between 1992 and 2003 from two large cohorts of HIV-infected patients in the U.S. (the Adult and Adolescent Spectrum of HIV Disease Project and the HIV Outpatient
Study). Of the 3550 incident cancers identified during 157,819 person-years of observation, 80% were AIDS-defining. During the study period, the incidence rates for Kaposi sarcoma and non-Hodgkin lymphoma decreased, whereas rates of anal cancer, prostate cancer, colorectal cancer, melanoma, and Hodgkin lymphoma all increased. The incidence of several non-AIDS-defining cancers was higher than that seen in the general population: Hodgkin lymphoma, melanoma, leukemia, and cancers of the anus, vagina, liver, lungs, oropharynx, kidney, and colon/rectum.

As expected, male-to-male sexual contact was a risk factor for Kaposi sarcoma and non-Hodgkin lymphoma, and coinfection with hepatitis B or C virus was a risk factor for liver cancer. A low nadir CD4 cell count was associated with increased risk for Kaposi sarcoma, non-Hodgkin lymphoma, cervical cancer, anal cancer, colorectal cancer, and lung cancer. Receipt of ART was independently associated with a decreased risk for Kaposi sarcoma, non-Hodgkin lymphoma, cervical cancer, breast cancer, colorectal cancer, and lung cancer.

Comment: Consistent with prior data, these studies demonstrate that HIV-infected patients have a higher incidence of several non-AIDS-defining cancers than does the general U.S. population. Although neither study provides much new information, they both remind us to be vigilant about risk reduction (through smoking cessation and other strategies) and early cancer detection.

— Sonia Nagy Chimienti, MD


Low CD4-Cell Counts — Not Just About OI Risk

In a cohort of patients receiving ART, lower CD4-cell counts increased the risk not only for AIDS-defining conditions but also for non-AIDS-defining disease.

Lower CD4-cell counts among HIV-infected people are associated with increased risk for AIDS-defining opportunistic diseases. The widespread use of combination antiretroviral therapy (ART) has decreased the frequency of these illnesses, resulting in longer survival and a relative increase in the rate of non-AIDS-defining conditions (AIDS Clin Care Nov 2006, p. 93, and J Acquir Immune Defic Syndr 2006; 43:27). To evaluate the link between low CD4-cell counts and non-AIDS diseases, investigators reviewed data from 1397 patients who initiated ART as part of the FIRST trial (median follow-up, 5 years).

As shown in the table below, higher latest CD4-cell count was associated with a lower rate of both AIDS and non-AIDS diagnoses. After adjusting for age, sex, race, current viral load, previous AIDS events, and hepatitis coinfection, researchers found that the risk for AIDS was lowered by 44% — and the risk for non-AIDS disease by 14% — with each 100-cell/mm³ increase in latest CD4 count.

Comment: Consistent with other studies, this analysis indicates that maintaining high CD4-cell counts reduces the risk not only for AIDS-defining conditions but also for non-AIDS-defining disease. Overall, the collective evidence suggests that it is time to revisit the recommendations for when to initiate ART.

— Charles B. Hicks, MD


Enhancing Antiretroviral Activity in the Brain

Receiving a combination of drugs that have strong penetration into the CNS reduces the likelihood of having detectable virus in the CSF.

Even in this era of effective HIV treatment, the central nervous system (CNS) remains an ominous black box. Some data suggest that rates of HIV-associated neurologic disease are as high as ever, but clinicians seldom consider drug penetration into the CNS when devising treatment regimens. Should they?

As a first step to answering this question, investigators from a nationwide research consortium sought to determine whether drug penetration into the CNS correlated with detectable virus in cerebrospinal fluid (CSF). Of 467 patients on ART between 2003 and 2006, 29% were receiving PI-based regimens, 37% were receiving NNRTI-based regimens, and the rest were receiving 3-drug or 2-drug NRTI combinations, for a total of 166 different drug combinations. For each combination, the researchers devised a “CNS penetration-effectiveness (CPE)” rank by using published data to estimate the CSF penetration of each individual drug as high (1 point), medium (0.5 points), or low (0 points) and then summing the results.

Forty-three percent of patients had detectable serum viral loads, but only 17% had detectable HIV RNA in CSF. A low CPE rank proved to be a risk factor for detectable CSF viral load, independent of plasma viral load, adherence, CD4-cell count, total number of drugs in the regimen, type of regimen, and duration of treatment.

Comment: These data make physiologic sense; the next question is whether drugs with high CSF penetration treat HIV-associated neurologic syndromes more effectively than others. That

| Rate of AIDS- and Non–AIDS-Defining Disease Among Patients Receiving ART, Stratified by Latest CD4-Cell Count |
|---------------------------------------------------------------|---------------------------------|---------------------------------|
| Latest CD4 Count (cells/mm³) | Rate of AIDS-Defining Disease (per 100 person-years) | Rate of Non-AIDS-Defining Disease (per 100 person-years) |
| <200 | 13.8 | 2.1 |
| 200–350 | 2.0 | 1.7 |
| >350 | 0.7 | 0.7 |
assumption also makes sense, and clinicians may wish to act on it, but unfortunately, much of the data behind the index used here comes from pharmacokinetic or nonclinical chemical studies and may be difficult to obtain and interpret. These authors would have done clinicians a service by supplying some examples of regimens with unusually high CPE ranks; unfortunately, they elected not to do so.

— Abigail Zuger, MD


**First-Line Therapy for HIV**

Virologic suppression is more likely with an efavirenz-based regimen than with a lopinavir/ritonavir-based one. First-line therapy for HIV infection usually consists of two NRTIs plus either the NNRTI efavirenz or a ritonavir-boosted PI such as lopinavir/ritonavir. Which of these two initial regimens is better? Also, NRTIs have been associated with toxicities such as lipoatrophy. Are regimens that do not include NRTIs as effective as ones that do? To answer these important questions, investigators randomized 757 HIV-infected, treatment-naive patients to receive one of three regimens: efavirenz plus two NRTIs (EFV group), lopinavir/r plus two NRTIs (LPV group), or lopinavir/r plus efavirenz (NRTI-sparing group).

The rate of virologic failure was 24% in the EFV group, 29% in the NRTI-sparing group, and 37% in the LPV group. Among patients with pre-treatment viral loads ≥100,000 copies/mL, the EFV group had a longer time to virologic failure than did the other groups. However, the LPV and NRTI-sparing groups had larger increases in CD4-cell count at week 96 than did the EFV group. Grade 3 or 4 laboratory abnormalities were most common in the NRTI-sparing group, mainly because of elevated triglyceride levels. Surprisingly, the median increase in limb fat was lower in the EFV group (0.05 kg) than in the LPV group or the NRTI-sparing group (0.7 kg and 1.15 kg, respectively). In patients who had virologic break-through, fewer patients in the LPV group than in the EFV group developed multiclass-resistant virus. Mutations associated with NNRTI resistance were more frequent in the NRTI-sparing group than in the EFV group.

**Comment:** This important trial of first-line therapy shows that the rate of virologic failure is lower in patients taking efavirenz-based regimens than in those taking lopinavir/r-based ones. However, in those patients who do have virologic failure, multiclass resistance develops more frequently with efavirenz-based regimens than with lopinavir/r-based ones. What are the take-home lessons? Efavirenz-based regimens are an excellent first choice for most patients with HIV infection. In patients who cannot tolerate efavirenz, lopinavir/r-based regimens are likely to be effective. Studies are ongoing to compare efavirenz-based regimens with combinations that include newer PIs or agents in novel classes. Much of the interest in NRTI-sparing regimens has faded since the inception of this study because rates of metabolic complications are lower with newer NRTIs than with older ones. — Rajesh T. Gandhi, MD

Dr. Gandhi is Assistant Professor of Medicine at Harvard Medical School and Director of HIV Clinical Services and Education at Massachusetts General Hospital in Boston.


**Salvage Treatment for PCP**

A review of 29 studies suggests that TMP-SMX is the best option, but several important factors still need to be addressed.

No definitive studies have been performed to determine the optimal management of AIDS patients who do not respond to first-line treatment for Pneumocystis jirovecii pneumonia (PCP). To address this gap, investigators conducted a systematic review of 29 studies that described second-line treatment for a total of 468 episodes of PCP. All but one of the studies were published between 1982 and mid-2007; the other was an unpublished case series from Europe that involved 82 HIV-infected patients who required second-line therapy for PCP between 1989 and 2004. Across the studies, all patients were HIV infected, had microbiologically proven PCP, and remained on their initial PCP regimens for at least 5 days before switching because of inadequate response. The outcome of interest was defined as survival or “definitive clinical improvement” as described by the original authors.

Overall, response to second-line therapy was similar with trimethoprim-sulfamethoxazole (TMP-SMX; 73%) and clindamycin-primaquine (68%) but was lower with pentamidine (44%); outcomes for atovaquone were favorable but not statistically significant because so few patients received it. Efficacy increased during the study period for both TMP-SMX (50% before 1989, 62% in 1989–1995, and 82% after 1995) and pentamidine (28%, 58%, and 52%, respectively), but it remained unchanged for clindamycin-primaquine.

Severity of disease at the time of switching could be assessed only in the European case series. Prognostic variables used in this analysis included partial pressure of arterial oxygen at admission, age, CD4-cell count, year of diagnosis, presence of bacterial coinfection, use of PCP prophylaxis, and clinical center, but not receipt of antiretroviral therapy. Three months after PCP diagnosis, risk for death was significantly higher in patients who received salvage therapy with intravenous pentamidine rather than with TMP-SMX (adjusted relative risk, 12.4); risk with clindamycin-primaquine was similar to that with TMP-SMX.

**Comment:** The authors concluded that TMP-SMX is the best approach for salvage treatment of PCP in AIDS patients. However, several important factors could not be addressed in this analysis, including initial severity of disease for most patients studied; the nonrandomized choice of initial treatment; and the more-severe, potentially life-threatening toxicities of intravenous pentamidine and its lack of activity against bacterial copathogens. Although the authors’ recommendation is limited by the fact that TMP-SMX is already the standard...
Chlamydia and Gonorrhea in MSM with Newly Diagnosed HIV

In this San Francisco study, 38% of MSM had gonorrhea, chlamydia, or both at the time of HIV diagnosis.

Sexually transmitted infections (STIs) are important risk factors for HIV infection. Ulcerative STIs, such as herpes, significantly increase the risk for HIV acquisition, but the association with nonulcerative STIs, such as gonorrhea and chlamydia, is not as strong. Nevertheless, these infections are prevalent among men who have sex with men (MSM) and are frequently asymptomatic. Consequently, the CDC recommends annual screening for gonorrhea and chlamydia among all sexually active MSM, independent of HIV status.

To examine the frequency of gonococcal and chlamydial infection among MSM being tested for HIV at STI clinics, investigators from the San Francisco Department of Public Health studied data from 6864 MSM who were not previously known to be HIV infected and who were tested for HIV at clinic visits between January 2004 and December 2006. The men were also tested for rectal, pharyngeal, and urethral gonococcal and chlamydial infections based on the types of sexual behavior reported, regardless of condom use.

Three percent of MSM were classified as having newly diagnosed HIV infection. These men were 2.4 times more likely than HIV-negative MSM to be infected with gonorrhea (26% vs. 11%) or chlamydia (19% vs. 8%); most of the STIs were rectal infections (53% for gonorrhea and 92% for chlamydia).

Approximately 58% of the HIV-infected men with gonorrhea and 37% of those with chlamydia received same-day treatment because of symptoms or reported contact with the infectious agents. Based on these findings, the authors have instituted presumptive gonorrhea and chlamydia treatment at their STI clinic for all MSM with newly diagnosed HIV infection.

Comment: Some readers may be surprised to learn that, although HIV is recognized as an STI, most STI clinics did not routinely test for HIV until recently. The data presented in this paper suggest that MSM with newly diagnosed HIV are likely to also have gonorrhea, chlamydia, or both, and the investigators propose that presumptive therapy be given without waiting for the results of gonorrhea or chlamydia testing. This strategy is appealing and may make sense in STI clinics that have large populations of MSM, but it remains to be proven as effective from a public health standpoint.

— Carlos del Rio, MD