Update on the Treatment of Acute and Early HIV Infection

I. Diagnosis of Acute HIV Infection

"UNFORTUNATELY, I THINK MOST HEALTH-CARE PROVIDERS DON'T QUITE understand why it’s important to diagnose primary HIV infection," Dr. Marty Markowitz began. "I think many health-care providers often say, well, come back in three months and we’ll test again. But I really do believe that diagnosing acute HIV infection has a number of advantages." The potential benefits discussed by Dr. Markowitz include early counseling, while someone is at their most infectious, with respect to HIV prevention. “Patients in the acute stages of HIV infection have very high viremia,” he said. “With really high HIV levels, what somebody may consider ‘safe sex’ may not necessarily be safe at all.” Early HIV diagnosis can also facilitate early entry into clinical care. What’s more, it can lend a big hand in epidemiological efforts to follow and curb the spread of HIV by helping to define the forces behind ongoing new infections. Early diagnosis can also contribute to research tracking the prevalence of drug-resistant virus transmission. Moreover, there is an ongoing need for additional research regarding the immunopathogenesis and the immediate treatment of primary HIV infection, which requires new patients to fill various study vacancies.

TABLE 1. Defining and Staging Acute and Early HIV Infection: The ADARC System

<table>
<thead>
<tr>
<th>Stage/duration</th>
<th>HIV-RNA</th>
<th>EIA</th>
<th>Western blot</th>
<th>Detuned EIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia — Acute (2 weeks)</td>
<td>Positive (&gt;5,000 copies/mL)</td>
<td>Negative</td>
<td>Negative</td>
<td>N/A</td>
</tr>
<tr>
<td>Ib — Acute (4 weeks)</td>
<td>Positive</td>
<td>+/-</td>
<td>Indeterminate</td>
<td>N/A</td>
</tr>
<tr>
<td>II — Early (120 days)</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>III (within six months)</td>
<td>Positive (negative within previous six months)</td>
<td>Positive</td>
<td>Positive</td>
<td>N/A</td>
</tr>
<tr>
<td>IV (within 12 months)</td>
<td>Positive (negative within previous 12 months)</td>
<td>Positive</td>
<td>Positive</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Source: Aaron Diamond AIDS Research Center
sense of these tests and their results, Dr. Markowitz reviewed the laboratory criteria used to define and stage acute and early HIV infection, at least for the purpose of study at the Aaron Diamond AIDS Research Center (ADARC). As illustrated in Table 1, there are two stages of acute HIV infection and three stages of early HIV infection. The interpretation of positive HIV-RNA assays—combined with the various possible results documented using EIA, Western blot, and detuned EIA—plays a formidable role in the diagnosis and staging of HIV infection during these important stages. With respect to HIV-RNA testing, Dr. Markowitz noted that ADARC uses a cutoff of 5,000 copies/mL. “When you do HIV-RNA testing and you get a result of 300 copies/mL, that’s not a positive HIV-RNA,” he said. “That’s probably an operator-mediated contamination. The test will need to be repeated. Don’t tell patient they’re infected if they have a negative antibody test and 300 copies/mL of HIV-RNA. You might be catching them on the way up, but that’s almost unheard of because most of the patients who are symptomatic have viral loads in the millions, not in the hundreds.”

**Theoretical Benefits of Treating Primary HIV Infection**

There are a number of theoretical benefits associated with initiating therapy during primary HIV infection. First, it may limit total body viral burden. If started early enough, antiretroviral treatment may limit the pool size of long-lived HIV-infected cells, such as memory CD4+ cells. Because these cells are rapidly seeded within days of infection, therapy needs to be initiated promptly and effectively to slow this process.

A second theoretical benefit of initiating therapy during primary HIV infection was discussed in some level of detail by Dr. Walker. If HIV were like other viruses, acute infection should elicit strong HIV-specific CD4+ cell activity, including robust lymphocyte proliferative responses (LPsR) to HIV antigens and, ultimately, broad stimulation of cytotoxic T-lymphocytes (CTLs). Yet, because HIV selectively infects activated CD4+ cells, it is believed that these cells become preferential targets for infection during the period when viral load is at its highest. Loss or dysfunction of these cells would ultimately impair immunologic activity needed to keep viral replication at bay, including activation of CTLs. The key then is to protect HIV-specific CD4+ cells during primary HIV infection, thereby augmenting their ability to respond to HIV and to maintain sufficient CTL activity.

Both Drs. Markowitz and Walker pointed out that clinical trials, examining whether treatment of primary HIV infection delays progression of disease, have not yet panned out and that more research in this area is needed. “Ultimately,” Dr. Markowitz said, “we’d like to determine if initiating therapy during primary HIV infection can delay progression of disease, delay the need to initiate long-term continuous therapy, or to limit the lifetime exposure to antiretroviral agents.”

**Recruitment at ADARC**

ADARC is one of eight units participating in the National Institutes of Health (NIH)-sponsored Acute Infection and Early Disease Research Program (AIEDRP). As of March 2004, a total of 263 subjects are enrolled in the AIEDRP program. According to Dr. Markowitz, 171 (65%) subjects remain active in the program; 138 are currently receiving antiretroviral therapy; and 33 are off treatment. “We’ve done really well over the past few years,” Dr. Markowitz added. “We’ve identified and enrolled 105 subjects since July 2001.”

**II. Prevalence of Transmitted Drug-Resistant HIV Variants**

There have been a number of studies describing the prevalence of HIV-drug resistance in newly infected individuals. At ADARC, however, Dr. Markowitz and his colleagues have been interested in tracking the temporal changes in transmitted drug resistance; that is, the epidemiology of transmitted drug resistance over time.

Dr. Markowitz highlighted data reported by Dr. Viviana Simon at a 2003 PRN meeting and published in the September 2003 edition of The PRN Notebook. The data involved 249 individuals who joined a primary HIV infection cohort at ADARC between 1995 and 2002 and were divided into three groups, according to the year of entry into the cohort. Group A consisted of 76 patients, enrolled between 1995 and 1998; group B consisted of 71 patients, enrolled between 1999 and 2000; and group C consisted of 102 patients, enrolled between 2001 and 2002. All patients were naïve to antiretroviral therapy at study entry, and genotypic and phenotypic resistance testing was performed on samples obtained before initiation of treatment.

The overall prevalence of any resistance-associated mutations in newly infected patients increased from 13% in group A to 20% in group B. Patients in group C actually reflected a downward trend in the prevalence, with approximately 17% presenting with at least one resistance-

**Figure 1. Changing Pattern of Transmitted Drug-Resistant HIV Strains**

Evidence of genotypic and phenotypic drug resistance among 249 individuals joining a primary HIV infection cohort between 1995 and 2002. Patients were divided into three groups, according to the year of entry into the cohort. Group A consisted of 76 patients, enrolled between 1995 and 1998; group B consisted of 71 patients, enrolled between 1999 and 2000; and group C consisted of 102 patients, enrolled between 2001 and 2002. As illustrated in the bar graph on the left, the overall prevalence of any resistance-associated mutations in newly infected patients increased from 13% in group A to 20% in group B. Patients in group C actually reflected a downward trend in the prevalence, with approximately 17% presenting with at least one resistance-associated mutation. Phenotypic resistance profiles are illustrated in the bar graph on the right. Reduced susceptibility to nucleoside reverse transcriptase inhibitors was only seen in group A. The prevalence of resistance to non-nucleoside reverse transcriptase inhibitors increased steadily over the three observation periods and evidence of reduced susceptibility to protease inhibitors, which was not documented in group A, remained below 5% in groups B and C. Multiple-drug resistance, documented by phenotypic testing, also remained below 5%, which is consistent with data from other cohort studies.

Source: Martin Markowitz, MD
associated mutation (see Figure 1). While this overall decrease can be tied to the decrease in transmitted nucleoside reverse transcriptase inhibitor (nrti) resistance, it’s also important to note an increase in the prevalence of non-nucleoside reverse transcriptase inhibitor (nnrti) and protease inhibitor (pi) resistance among patients in group C.

In terms of phenotypic resistance testing—resistance was defined as a greater than fivefold reduction in susceptibility to any antiretroviral drug—nrti resistance was only seen in group A. Between 1999 and 2002, no virus with more than fivefold reduced susceptibility to any nrti was seen, with the exception of multi-drug resistant variants. In other words, Dr. Markowitz’s group observed the transmission of viruses with altered genotypes—compatible with previous thymidine analogue exposure (e.g., mutations conferring resistance to zidovudine)—but with drug-sensitive phenotypes. More specifically, 50% of the patients identified in 1999 and 2000 who had evidence of genotypic resistance to nrtis, but no evidence of phenotypic resistance to this class of drugs, had virus harboring the T215D/S mutation in the reverse transcriptase gene.

As for reduced phenotypic susceptibility to nrtis, the prevalence increased steadily over the three observation periods. Phenotypic resistance to PIs, which was not reported in group A, remained below 5% in groups B and C. Multiple-drug resistance, documented by phenotypic testing, also remained below 5%, which is consistent with data from other cohort studies.

Recent Data

Dr. Markowitz and his group at AARC have recently analyzed data involving 66 patients enrolled in 2003. Approximately 15% of the patients had viruses with evidence of resistance to at least one nrti, he explained, “and almost 20% of patients we’re seeing now are highly resistant to nrtis at baseline. This is alarming, as this has been an annual increase over the past several years. It reflects efavirenz use and efavirenz failure in the community and transmission of efavirenz-resistant virus. This will have a profound effect on these patients’ responses to efavirenz-based regimens. Variants harboring K103N and some of the other mutations are the gifts that keep on giving. They do not revert to wild type and they are archived.” In 2003, seven of the 66 patients entering the acute/early HIV infection program at AARC had documented multiple-drug resistance, defined as resistance to at least two classes of antiretrovirals. “Two of these patients had triple-class resistance,” Dr. Markowitz added. “And for the first time this year, I’ve seen two patients with essentially untreatable virus.”

Replication Characteristics of Transmitted Drug-Resistant HIV

Could the transmission of drug-resistant virus actually serve as an advantage to a recently infected person? After all, the paradigm of drug resistance says that the more drug resistant the virus is, the less replication competent it should be. However, the AARC group speculated that since some drug-resistant mutants are successfully transmitted, they might have different characteristics and that they are possibly more efficient in establishing infection.

To test this hypothesis, Dr. Markowitz’s group cultured nine drug-resistant and nine drug-sensitive isolates from PBMCs, collected from 18 patients who presented within 10 to 79 days after onset of acute retroviral symptoms (Simon, 2003). Three in vitro assays were used: one single-cycle assay using reporter cell lines to measure infectivity of the isolates, a second in which parallel infection of CD4+ cells was performed to measure the growth kinetics of the isolates, and a third single-cycle assay, developed by ViroLogic, to measure the replication capacity of recombinant viruses encoding only the protease and reverse transcriptase regions from the patients’ isolates.

Using the first assay, Dr. Markowitz’s team found that the drug-resistant variants had higher measured infectivity than wild-type strains; two multiple-drug-resistant viruses and one protease inhibitor-resistant virus performed best (see Figure 2). Using the growth kinetics assay, drug-resistant isolates replicated as efficiently over multiple rounds of replication in CD4+ cells as wild-type virus. Again, the multiple-drug resistant variants and one of the protease inhibitor-resistant variants had better growth kinetics, while growth kinetics of the other drug-resistant isolates were similar to wild-type virus. As for the third assay, drug-resistant virus had a significantly lower assay value compared to wild-type virus. A likely reason for this is that functional regions outside of the mutated protease and reverse transcriptase genes essentially help the virus to overcome any limitations in infectivity and growth kinetics.

III. Benefits of Early Initiation of Antiretroviral Therapy:

Can it be Demonstrated?

With the twilight of the HIV eradication hypothesis, which stemmed from research conducted at AARC suggesting that hitting HIV “hard” and “early” could potentially clear the body of HIV in as little as one-and-a-half to three years of therapy, the possibility of initiating potent, yet short-term, antiretroviral therapy during primary HIV infection to achieve long-term control of infection in the absence of therapy remains a worthwhile goal. While many clinicians are currently locked into the debate regarding when to start treatment and which drugs to start with, the end result is still the same: the long-term use of antiretroviral drug combinations, none of which is risk-free. If ongoing research is able to demonstrate with certainty that the short-term use of potent antiretroviral therapy initiated during primary HIV infection is associated with remission, then it will have achieved a breakthrough unsurpassed by treatment at any other later stage of disease. The question remains, however: will clinical benefits associated with early initiation of antiretroviral therapy be demonstrated?
The AIEDRP Treatment Discontinuation Study

Some preliminary data from the AIEDRP, evaluating whether antiretroviral therapy during primary/early HIV infection is associated with improved outcomes after treatment discontinuation, were reported by Dr. Rick Hecht at the 10th Conference on Retroviruses and Opportunistic Infections, held in Boston in February 2003 (Hecht, 2003). This was a retrospective analysis of 231 subjects enrolled in the AIEDRP database. Sixty-two of these patients were treated with antiretroviral therapy, for a mean of 77 weeks, and 169 remained untreated. Dr. Hecht’s group analyzed viral load and CD4+ cell count data after 24 weeks among 34 primary/early HIV infection-treated patients who discontinued therapy, and compared them with viral load and CD4+ cell count data, 24 weeks post-diagnosis, among 34 patients who did not receive treatment.

Approximately 14% of the patients in the untreated group had been infected for less than six weeks, compared to 31% of the patients in the treated group. Conversely, 63% of patients in the untreated group had been infected for longer than 12 weeks, compared to 19% of patients in the treated group. At baseline, the average viral load was 4.02 log_{10} copies/mL in the untreated group, compared to 4.96 log_{10} copies/mL in the treated group; baseline CD4+ counts were 578 and 513 cells/mm^3 respectively. “There was a skew in the treated patients in terms of earlier infection, higher viral load, and slightly lower CD4+ cell counts,” Dr. Markowitz pointed out.

In terms of the mean viral load at 24 weeks, the unadjusted analysis demonstrated an average HIV-RNA level of 3.82 log_{10} copies/mL in the treated patients and an average HIV-RNA level of 4.0 log_{10} copies/mL in the untreated patients. However, in the adjusted analysis, which factored in differences in baseline variables, an average HIV-RNA level of 3.57 copies/mL was documented in the treated patients 24 weeks after discontinuing therapy, compared to an average HIV-RNA level of 4.11 log_{10} copies/mL in the untreated patients. The comparison between the treated and untreated patients, in the adjusted analysis, was statistically significant.

As for CD4+ counts, the unadjusted analysis yielded a mean of 668 cells/mm^3 in the treated group and a mean of 543 cells/mm^3 in the untreated group. These data were statistically significant. In the adjusted analysis, CD4+ count levels were 686 cells/mm^3 in the treated group and 576 cells/mm^3 in the untreated patients. “The adjusted analysis was even more statistically significant than the unadjusted analysis,” Dr. Markowitz commented. “There was definitely a CD4+ cell count benefit. But it’s soft. And this study really helped us to set the stage for a randomized clinical study to prove that there’s a benefit in using antiretroviral therapy in patients who are in the early stages of HIV infection.”

To corroborate these initial findings, Dr. Walker’s group conducted another, slightly larger and significantly longer study involving 14 patients. All of these patients were HIV antibody-negative and had high HIV-RNA levels prior to beginning treatment. Prior to initiating their first of up to four STIs, patients maintained HIV-RNA levels below 50 copies/mL for at least eight months. And much like the eight-patient pilot study, patients were required to restart treatment if their viral load exceeded 5,000 copies/mL for three consecutive weeks or if viral load exceeded 50,000 copies/mL at any one time.

Initial reports from this study, reported in the September 2001 issue of the Notebook, suggested that STIs were resulting in improved immune control in 7/14 (50%) patients. Much-awaited long-term follow-up data were recently reported at the 11th Conference on Retroviruses and Opportunistic Infections, held in San Francisco in February. Dr. Walker reviewed these follow-up data, once again, at the April PRN meeting.

The 14 patients in this STI study were followed for up to 5.3 years. Only one patient (patient AC-10) maintained control of viral replication since stopping therapy the first time. A second patient (AC-02) restarted therapy due to virologic rebound during the first STI, but has remained off therapy since initiating his second treatment interruption. And a third patient (AC-14), having been required to start therapy again a second time, has maintained a low viral load since initiating a third STI. No additional evidence of virologic control was seen in patients initiating a fourth STI.

Looking at the study group as a whole, Dr. Walker explained that 11/14 (78.6%) patients were able to maintain immunologic control of viremia for at least 90 days. However, only 6/14 (43%) were able to maintain control at one year, and only 3/14 (31%)—the three patients discussed in the preceding paragraph—were able to maintain virologic control for more than three years.

It should be noted that in a Kaplan-Meier evaluation of the time for HIV-RNA to reach greater than 30,000 copies/mL, 40% of the 14 patients who initiated treatment interruptions had less than 30,000 copies/mL at 900 days, compared to a control cohort of approximately 25%.

Dr. Walker pointed out that, looking at the group as a whole, the rate of CD4+ cell count loss when antiretroviral therapy was stopped was very similar to the rate of loss seen in patients with chronic HIV infection, using data published by Dr. John Mellors and his colleagues for the comparison (Mellors, 1997). And among the 14 patients with the most rapid declines in CD4+ cell counts upon stopping treatment, the rate of loss appeared to be no different when compared to data involving patients with chronic HIV infection undergoing STIs (Tebas, 2002). During the longest of the four treatment interruptions, the median CD4+ count was 753 cells/mm^3 at the start of the treatment interruption and the median CD4+ count was 511 cells/mm^3 at the end of the treatment interruption.

As for factors that may have predicted the control of HIV-RNA, specific HLA alleles did not appear to be associated with virologic control, nor did CCR5 status, CCR2 status, G640C co-infection, the time since onset of symptoms, the degree of seroconversion, or the viral load at the start of treatment.

Looking at markers of cellular immunity, Dr. Walker noted that the breadth and magnitude of HIV-specific CTL activity increased during the STIs, but these increases did not correlate with control of viremia. We saw that increasing time off therapy increased both the breadth and the magnitude of CD8+ T-cell responses,” Dr. Walker noted. “However, neither the breadth nor magnitude of these responses could help us predict the time to virologic failure.”

During the question-and-answer period following Dr. Walker’s presentation, Dr. James Braun asked if there were any differences in virologic control among patients who may have started antiretroviral therapy

The Massachusetts General Hospital Experience

In an initial study reported by Drs. Eric Rosenberg, Walker, and their colleagues at Massachusetts General Hospital, eight patients who began therapy during acute HIV infection agreed to initiate one or two structured treatment interruptions (STIs), with the plan to restart therapy if viral load exceeded 5,000 copies/mL for three consecutive weeks or exceeded 50,000 copies/mL at any given time (Rosenberg, 2000). Despite rebound in viremia, all eight patients were able to achieve at least a transient steady-state off therapy with viral loads below 5,000 copies/mL. At the time the report was prepared for publication in Nature, five out of eight subjects remained off therapy with viral loads less than 500 copies/mL after a median of six-and-a-half months. Dr. Rosenberg’s group observed increased virus-specific CTLs and maintained HIV-specific CD4+ cells in all eight patients.
sooner after the time of infection than those who perhaps started later, a
suggestion that, perhaps, the window of therapeutic opportunity during
acute HIV infection is much smaller than believed. However, Dr. Walker
pointed out that immunologic control, at least among these 14 patients,
did not appear to be associated with the time of therapy initiation.

**Additional ADARC Experience**

**IN A STUDY CONDUCTED AT ADARC, INDEPENDENT OF THE AIEDRP NETWORK, Dr. Markowitz and his group treated 16 patients with antiretroviral therapy within 120 days of the onset of symptoms of newly acquired HIV infection (Markowitz, 2002). Eleven of the 16 participated in an adjunctive therapeutic vaccine trial involving a recombinant canarypox vaccine (vCP1452). After a mean of 3.2 years of treatment, they elected to discontinue therapy. HIV-RNA rebounded in all subjects, but this was followed by a spontaneous, transient although significant reduction in HIV-RNA, with declines ranging from 0.3 to 3.1 log10 copies/mL. “Even though there was evidence of HIV-specific cell-mediated induction,” Dr. Markowitz added, “viral load was not persistently suppressed in any subject, although we did see transient reductions in viral load. People often ask me, why is this data so different from other results, including the study conducted at Massachussetts General Hospital? Well, the fact is, the data aren’t really different. If we follow patients long enough, viral rebound does happen. In both studies, there seems to be some nice virologic control early on after discontinuing therapy. But then the virologic control is lost. So, really, the results are more similar than they are different.”

**Acute HIV Infection and the Potential of Cyclosporine**

**THIS IS NOT TO SAY THAT ADARC AND THE REST OF THE AIEDRP NETWORK are not currently developing studies evaluating treatment modalities during acute HIV infection. As explained by Dr. Markowitz, acute HIV infection is characterized by massive dissemination of HIV—“HIV-RNA levels are often in the millions,” he pointed out—immune activation, including the release of proinflammatory cytokines, which increases the numbers of susceptible cells and promotes viral replication; and immunodeficiency, including direct cytopathic effects of HIV and apoptosis due to immune activation. “What we want to do is to somehow block these early events,” Dr. Markowitz said. “Actually, we think this is something we might be able to do. And this is where our interest in cyclosporine A comes in.”

Simply put, cyclosporine A (CsA) is an immunosuppressant that modulates the activation of CD4+ cells. More specifically, CsA binds to cyclophilin (CpN) in the cytoplasm of cells, forming a complex between CsA and CpN. This CsA/CpN complex binds to and blocks the function of the enzyme calcineurin (CnN), which in turn blocks the transport of the nuclear factor of activated T-cells (NF-ATc) to the cell’s nucleus. If NF-ATc does not reach the nucleus, it cannot bind with the nuclear component of the nuclear factor of activated T-cells (NF-ATs). It is this NF-ATc/NF-ATs complex that is necessary to initiate IL-2 production. And without sufficient IL-2 production, CD4+ cells will not be activated, potentially reducing the inflammatory response to HIV infection and the proliferation of viral replication.

The hypothesis of AI 501, another AIEDRP study in the works, is that CsA, given with antiretroviral therapy during acute HIV infection, will reduce the size of the latent pool of HIV-infected cells and preserve both HIV-specific and non-HIV-specific immunity due to sparing of CD4+ cells by preventing activation and infection. Approximately 50 patients will be randomized in a 2:1 fashion. Patients will need to be HIV negative or present with three bands or less on a Western blot. Patients will also need to have HIV-RNA levels in excess of 500,000 copies/mL. All patients will receive lopinavir/ritonavir plus abacavir/zidovudine/lamivudine (Trizivir). Two-thirds of the patients will also receive CsA, 0.3 mg/kg twice daily for four weeks. The primary end-point is the level of proviral DNA at 48 weeks and the secondary end-points include absolute CD4+ cell counts at various time points and measures of HIV-specific immunity.

There are data to back the rationale of AI 501. In one study reviewed by Dr. Markowitz, the virologic and immunologic effects of immunomodulation during primary simian immunodeficiency virus (SIV) infection were examined in monkeys (Martin, 1997). The animals were treated with either cyclosporine or placebo for 32 days, beginning five days before SIV inoculation. Duration of antigenemia decreased in 5/7 treated monkeys, with two monkeys experiencing delayed onset and peak of antigenemia. Proviral DNA levels in blood and lymph nodes, along with infected cell numbers in lymph nodes, were also transiently decreased. What’s more, transient increases in CD4+ cell counts were seen in the cy-
cyclosporine-treated monkeys, compared to those in the control group.

Data are also available from a study involving humans with acute HIV infection (Rizzardi, 2002). In this study, a Swiss team evaluated the safety and the immune-modulating effects of combining CsA (0.3 to 0.6 mg/kg every 12 hours) with antiretroviral therapy in nine patients with primary HIV infection. After eight weeks of treatment, all patients discontinued the cyclosporine but remained on antiretroviral therapy.

Viral replication was suppressed to a comparable extent in the CsA-treated patients and in 29 control patients whose primary infection was treated with antiretroviral therapy alone. No differences in cell-associated DNA or RNA were seen in the two groups. Patients in the CsA group experienced significantly higher CD4+ cell counts, both during the initial eight-week regimen and up to a year later. What’s more, patients in the CsA group had higher HIV-specific CD4+CCR7- cells—effector memory cells—than those treated with antiretroviral therapy alone.

Other Immune-Based Therapies

MUCH LIKE ITS EFFORTS WITH CSA, THE AIEDRP IS HOPING TO STUDY other interventions to enhance immune control during acute HIV infection. Interventions being explored include therapeutic vaccination, using the Merck polyvalent Ad-5 vaccine and the ADARC polyvalent MVA vaccine to augment cell-mediated immune responses. “We will be taking our patients who have been on antiretroviral therapy for prolonged periods of time, vaccinating them, and seeing what happens when we take them off antiretroviral therapy,” Dr. Markowitz explained.

Another intervention that has made something of a comeback in recent years is humoral (antibody) control of residual viremia. “Early on, it was believed that antibodies were really important in terms of controlling HIV infection. But then it became pretty clear that antibodies weren’t doing much. But antibodies are again being taken seriously. Neutralizing antibodies do exist in HIV infection, but HIV is always escaping. In recent years, we’ve been learning a lot more about synthetic monoclonal antibodies and we now have a hypothesis that combinations of neutralizing antibodies, infused intravenously, will prevent detectable viremic rebound in patients with very low residual viral burden.”

The three monoclonal antibodies the AIEDRP are most interested in are 2G12, 2F5, and 4E10. “We have tested 91 isolates for susceptibility to neutralization by these particular antibodies,” he explained. Of these 91 isolates, 80% of them were neutralized by 2F5. Neutralization was defined as having an IC50 of less than 50 mg/mL, with the average IC50 of 9.6 mg/mL. This concentration, Dr. Markowitz explained, is easily achievable by intravenous infusion. The monoclonal antibody 4E10 neutralized 100% of the isolates which, like 2F5, targets epitopes in hiv-1 gp41. 2G12 was a bit more disappointing, as only 37% of the isolates were neutralized by this monoclonal antibody.

In vivo data involving these monoclonal antibodies, either alone or in combination with each other, have been presented. In one study, passive immunization with 2F5 appeared to prevent both intravascular and intravaginal SIV infection in chimpanzees (Conley, 1996). Another study using 2F5 and 2G12 prevented intravaginal infection in macaques (Mascola, 2000). 2F5 and/or 2G12 also appeared to delay the onset of infection with a chimeric SIV/HIV (SHIV) in macaques (Mascola, 1999), and reduced the risk of intrapartum SHIV transmission, also in macaques (Baba, 2000; Hoffmann-Lehmann, 2001). Also of interest are encouraging results from a study employing 2FS, 2G12, and 4E10 to prevent oral infection via blood and breast milk containing SHIV in neonatal macaques (Ferrantelli, 2003).

While data are not yet available from human studies, a pilot clinical trial involving these three monoclonal antibodies is in development at ADARC. It is a phase 1/II safety and efficacy trial of a combination of 2G12, 2F5, and 4E10 as an adjunct to antiretroviral therapy in patients treated during either the acute or early stages of HIV infection. It will enroll 12 patients and will be open-label in design. Patients who initiated therapy during the acute or early stages of HIV infection and have maintained undetectable viral loads for at least two years will receive three weekly infusions of the monoclonal antibodies and then stop antiretroviral therapy. Infusions will continue on a weekly basis for 12 weeks in the absence of antiretroviral therapy, and antiretroviral therapy will be restarted after 12 weeks if patients remain aviremic (HIV-RNA <50 copies/mL). The primary endpoint will be the number of patients remaining aviremic after 12 weeks off antiretroviral therapy, and the secondary endpoints include safety parameters, the characterization of rebounding viremia (e.g., neutralization profile and the source), and early events in the gut-associated lymphoid tissue.

Conclusion

DRS. MARKOWITZ AND WALKER ARE BOTH IN AGREEMENT THAT, DESPITE suboptimal results from primary HIV infection studies completed to date, the issue—as a matter of scientific inquiry and potential clinical benefit—is by no means dead in the water. Clinical trials to further explore primary HIV infection, as a therapeutic window of opportunity, are still planned and very much anticipated. For this reason, along with the established benefits of diagnosing HIV-infected individuals early in the course of disease and linking them with care, clinicians should continue to be on the watch for patients in the initial stages of HIV infection for the sake of advancing this research, safeguarding public health, and protecting the health of newly infected individuals.

References


