A publication of the
International AIDS Society-USA

IMPROVING THE
MANAGEMENT OF
HIV DISEASE

IN THIS ISSUE –
Recent Advances in

• New Nucleosides and Nonnucleoside RTIs
• Pathogenesis of HIV
• Protease Inhibitors
• Pediatric HIV Disease

VOLUME 3 ISSUE 2 AUGUST 1995
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This is the second of a series of publications derived from programs sponsored in 1995 by the International AIDS Society-USA (IAS-USA). For the third consecutive year, IAS-USA has sponsored such educational programs for clinicians and practitioners on a nationwide basis under the title of "Improving the Management of HIV Disease: An Advanced Course in HIV Pathogenesis, Antiretrovirals, and the Prevention of Opportunistic Diseases." This publication is derived from meetings in New York and Chicago. It covers topics in new antiretroviral agents and approaches (including newer nucleoside and nonnucleoside agents and protease inhibitors), pathogenesis of HIV disease, and issues in children and adolescents with HIV.

IAS-USA is a 501(c)(3) nonprofit organization committed to improving the treatment, care, and quality of life of persons with HIV disease through balanced and relevant information for physicians that is particularly intended to bridge clinical research and patient care.

IAS-USA has sought funding through the pharmaceutical industry with the goal of obtaining support from companies with competing products. Unrestricted educational grants have been provided by Bristol-Myers Squibb, Burroughs Wellcome Co, and Roche Laboratories. These companies have shown a continued commitment to support of such educational efforts and the IAS-USA is grateful for the support; IAS-USA is also grateful for the additional support for the Chicago program provided by Abbott Laboratories. None of the companies providing grant support have any influence or control over the selection of speakers or the content of presentations.

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NEW NUCLEOSIDE ANALOGUES AND NONNUCLEOSIDE RTIs

New nucleoside reverse transcriptase inhibitors (RTIs) and nonnucleoside RTIs (NNRTIs) were discussed at the New York meeting by Gerald H. Friedland, MD, from Yale New Haven Hospital and Yale University School of Medicine, New Haven, Connecticut, and at the Chicago meeting by John C. Pottage, Jr, MD, from Rush Medical College, Chicago, Illinois.

Despite enthusiasm over nucleoside analogue anti-HIV agents, the nucleoside RTIs remain the mainstay of antiretroviral therapy for the foreseeable future. There are several reasons for the continued interest and reliance on these agents. Available nucleoside RTIs have presently been limited in application because of dose-related toxicities, although further development of agents in this class may result in agents that retain the antiviral activity with less toxicity. In addition, some of the newer agents have characteristics that render them attractive as alternative treatment options. Finally, with the advent of the era of combination therapy, the nucleosides are likely to be utilized as the core of combination regimens as the characteristics of the newer classes of agents (eg, NNRTIs and protease inhibitors) are more clearly defined. Thus, it will remain important to know which of the nucleosides are most beneficial, least toxic, and most durable in effects in terms of both combination therapy and monotherapy.

Stavudine

Stavudine (d4T) was the fourth nucleoside analogue RTI to become available in the United States. Approval, based on data from studies of more than 11,000 largely zidovudine-experienced patients, indicated a beneficial effect on virologic and immunologic markers. Stavudine is characterized by rapid oral absorption, high absolute bioavailability that is unaffected by pH, absence of significant accumulation, and significant penetration into the cerebrospinal fluid (20% to 70%). Dose-ranging studies showed dose-proportional antiviral effects and dose-related toxicity, with the primary toxicity being peripheral neuropathy. These studies suggested an appropriate clinical dosage of 0.5 to 1.0 mg/kg, although investigation of higher dosages continues on the basis of postlicensure experiences that have indicated that toxicities, particularly peripheral neuropathy, are not so frequent as suggested in the early studies.

Several early-phase studies of stavudine indicated that treatment at doses of 0.5 to 1 mg/kg/d resulted in improvements in CD4+ cell count and HIV p24 antigen level that were sustained for 24 to 36 weeks, with a decrease in peripheral blood mononuclear cell (PBMC) viral titer of 0.5 to 2 logs being observed in the small number of cases. More recently, stavudine 40 mg bid was compared with zidovudine 200 mg tid in a double-blind, randomized trial sponsored by Bristol-Myers Squibb (BMS 019) in patients with CD4+ cell counts of 50 to 500/µL who had received more than 6 months of prior zidovudine. Among the 822 patients enrolled, the median CD4+ cell count was 235/µL and the mean duration of prior zidovudine treatment was 88 weeks.

Preliminary findings of the study were discussed by Dr Pottage at the Chicago meeting. A comparison of CD4+ cell count responses in the first 359 patients enrolled in the study showed that the difference between changes in CD4+ cell count significantly favored stavudine treatment over continued zidovudine over the course of the study. As stated by Dr Pottage, treatment failure in the protocol was defined as a 50% decline in CD4+ cell count, occurrence of an AIDS-defining event, or death. Data on the entire patient population, with follow-up of up to more than 2.5 years, revealed a number of findings favoring the switch to stavudine. Stavudine patients remained on drug for an average of approximately 79 weeks whereas zidovudine recipients remained on drug for approximately 50 to 55 weeks—a significant difference— with the primary reason for premature zidovudine discontinuation being the occurrence of clinical events.

In BMS 019, the switch to stavudine was associated with a significantly decreased rate of treatment failure compared with continued zidovudine in patients with more than 6 months prior zidovudine treatment; no significant difference in mortality was observed.

The rate of treatment failure (CD4+ cell count decline >50% of baseline and progression to clinical endpoints) among stavudine recipients was significantly lower than that among patients receiving continued zidovudine. Analysis of clinical progression—that is, reaching clinical endpoints alone— also showed that stavudine treatment was significantly superior to continued zidovudine, although the difference between the two groups was reduced somewhat compared with that for overall failure rate. Although the mortality rates in the two groups were not significantly different, a difference favoring stavudine treatment approached significance (P = 0.07).

Data from the entire patient population showed that peripheral neuropathy occurred significantly more frequently among stavudine recipients, being observed in 18 (4%) of 405 stavudine patients and 56 (13%) of 417 zidovudine patients (P = 0.0005). According to Dr Pottage, stavudine was better tolerated with regard to other adverse events, including gastrointestinal events and hematologic toxicity. According to data on the first 389 patients enrolled, presented by Dr Friedland, there were significant differences favoring stavudine in terms of hematologic abnormalities, with incidence of other laboratory abnormalities in the two groups being similar: hemoglobin levels of <11 g/dL developed in 5% of stavudine patients and 11% of zidovudine patients (P = 0.01); white blood cell counts of less than 4000/µL developed in 62% and 76%, respectively (P = 0.001); and polymorphonuclear cell counts of less than 1500/µL developed in 29% and 48%, respectively (P = 0.0001). The use of a standard-
Table 1. Risk Factors for Peripheral Neuropathy in the Stavudine Parallel Track Program

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative risk</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose, 40 mg:20 mg</td>
<td>1.39</td>
<td>1.26, 1.53</td>
<td>0.0001</td>
</tr>
<tr>
<td>Prior neuropathy</td>
<td>1.68</td>
<td>1.52, 1.86</td>
<td>0.0001</td>
</tr>
<tr>
<td>CD4+ count, baseline*</td>
<td>1.03</td>
<td>1.01, 1.04</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hemoglobin ≤11 g/dL</td>
<td>1.23</td>
<td>1.10, 1.38</td>
<td>0.0005</td>
</tr>
<tr>
<td>Male</td>
<td>1.33</td>
<td>1.04, 1.71</td>
<td>0.02</td>
</tr>
<tr>
<td>Karnofsky index &lt;80</td>
<td>1.13</td>
<td>1.02, 1.27</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Square root scale—eg, 25 cells vs 16 cells. CI indicates confidence interval.

Although these analyses are open to serious bias, they have at least suggested that a head-to-head comparison of the two agents is warranted. Such a comparison is planned in ACTG 298, in which patients with CD4+ cell counts of 200 to 600/μL who have not received prior antiretroviral therapy will receive stavudine, zidovudine, or the combination of the two. Outcome measures will include viral load and CD4+ cell count responses, development of resistance, and the possibility of pharmacologic interaction.

Some early in vitro pharmacologic data suggested potential pharmacologic antagonism between stavudine and zidovudine through competition for intracellular phosphorylating enzymes. However, more recent data from a number of laboratories evaluating in vitro antiretroviral activity of the combination indicate not only absence of antiviral antagonism but an additive or synergistic effect of the two under most conditions. Data from

![Graph 1](image1)

![Graph 2](image2)

Figure 1. Top: Mean CD4+ cell count change during stavudine treatment among a small population of zidovudine-naive patients (red line) and the larger population of zidovudine-experienced patients (black line) in the stavudine study data base (BMS 002, 003, and 006). Bottom: Mean change in CD4+ cell count among 31 zidovudine-naive patients receiving stavudine (red line) in BMS 002, 003, and 006 and 93 zidovudine-naive zidovudine recipients (black line) in ACTG 116A matched for CD4+ cell counts ≤300/μL.
the combination arm of this trial will help to determine if the combination will be of clinical utility. A trial comparing the two agents alone and in combination in symptomatic pediatric patients with little or no prior treatment is currently underway (ACTG 240).

One potential benefit of stavudine is that resistance to the agent, although apparently inevitable and demonstrably inducible in serial passage in culture, appears to develop quite slowly despite the relatively strong antiviral activity of the agent. Currently, there are few data on development of resistance in the clinical setting, and more systematic study is warranted. Although, as with other nucleoside analogues examined, there is a time-limited effect of stavudine on immunologic and virologic measures, decreased susceptibility of virus appears to be infrequent and of small magnitude.

As shown in Table 2, study of pretreatment and posttreatment isolates from 11 patients receiving 18 months of treatment in BMS 006 showed decreased susceptibility in two of the posttreatment isolates, with sensitivities of these isolates nevertheless remaining within the range of therapeutically achievable concentrations. No genetic basis for the decreased sensitivity was determined, suggesting that the susceptibility change in PBMC was an artifact, resulting from the rapid growth characteristics of the later virus in PBMC. An interesting finding was that five of the patients yielded zidovudine-resistant virus after 18 months, with no stavudine cross-resistance being observed; the authors of the study concluded that off-study administration of zidovudine had probably occurred. Another analysis of isolates from eight patients from BMS 009 after 12 months of treatment showed decreased sensitivity in one posttreatment isolate. The mean stavudine 50% effective dose (ED50) for the remaining isolates was unchanged after 52 weeks of treatment. As related by Dr Pottege, future ACTG studies of stavudine include ACTG 290, which evaluates stavudine vs didanosine vs zidovudine plus stavudine or didanosine in patients with CD4+ cell counts of 300 to 600/µL and greater than 12 weeks of prior zidovudine and ACTG 298, which evaluates stavudine vs zidovudine vs the combination of the two in patients with CD4+ cell counts of 300 to 600/µL and no prior nucleoside analogue RTI therapy. Dr Friedland identified a number of questions regarding the role of stavudine in therapy (see Table 3).

**Lamivudine**

Currently there is great interest in the therapeutic potential of lamivudine (3TC). Preclinical findings indicate that the agent has activity against both HIV-1 and HIV-2, including zidovudine-resistant strains, and exhibits no inhibition of hematopoietic progenitor cells. In vitro, the agent is less active than zidovudine and zalcitabine and more active than didanosine, and exhibits synergy with zidovudine. Lamivudine is markedly less toxic to host cells than either zidovudine or zalcitabine, exhibiting a favorable cytotoxicity profile comparable to that of didanosine. Phase I studies demonstrated that the drug is rapidly absorbed after oral administration, with high absolute bioavailability and no effect of food on overall absorption. It exhibits a serum half-life of 2 to 4 hours and a protracted intracellular half-life of approximately 12 hours. Elimination is primarily renal in the form of unchanged drug (approximately 70%). High-level resistance to lamivudine develops rapidly in vitro in association with a single amino acid substitution at RT codon 184. Although most information on lamivudine resistance has come from in vitro studies, resistance emerges uniformly within weeks in the clinical setting. The full implications of resistance in vivo have yet to be elucidated. Observations in this area thus far include: (1) maintenance of virologic response despite presence of resistance, (2) an interaction with zidovudine in the setting of combination therapy whereby zidovudine resistance may be delayed and whereby zidovudine-resistant virus may revert to susceptibility, and (3) continued susceptibility of isolates with the codon 184 mutation to zidovudine and stavudine in the absence of other RT codon changes.

Dr Friedland summarized initial findings in two North American (NUCA) and two European (NUCB) pivotal lamivudine phase II/III trials in adults; each program included one study.

### Table 3. Stavudine: Unanswered Questions

- Will existing studies demonstrate clinical benefit for stavudine?
- What is the role of stavudine in early therapy?
- Will the relative lack of development of resistance hold up over time?
- Can stavudine be combined with zidovudine and other antiretroviral agents with similar toxicities?
- What is the role of stavudine in combination therapy?
- What combinations offer the most sustained benefits and least toxicity?

### Table 2. Stavudine Resistance

- Limited in vivo information
- 11 pairs from BMS 006 treated for 18 months*
  - 9/11 posttreatment isolates unchanged
  - 2/11 posttreatment isolates had decreased sensitivity
  - Genetic basis of decreased sensitivity not determined
  - 5/11 developed zidovudine resistance
- 8 pairs from BMS 009 treated for 12 months
  - 1/8 posttreatment isolates had decreased ED50 (0.2 to 1.2 mM)

in zidovudine-naive patients and one in zidovudine-experienced patients. In NUCA 3001, 364 patients with 4 weeks or less prior zidovudine and CD4+ cell counts of 200 to 500/µL were randomized to double-blind treatment with lamivudine 150 or 300 mg bid plus zidovudine 200 mg tid or monotherapy with lamivudine 300 mg bid or zidovudine 200 mg bid. Data on mean actual changes in CD4+ cell count showed that response in the combination treatment arms was markedly better than that in the monotherapy arms, with counts remaining above baseline levels for at least 52 weeks in the former.

In NUCB 3001, 129 patients with CD4+ cell counts of 100 to 400/µL and 4 weeks or less of prior zidovudine were randomized to double-blind treatment with zidovudine 200 mg tid or zidovudine plus lamivudine 300 mg bid. After 24 weeks, all patients receiving zidovudine alone had lamivudine added to treatment. CD4+ cell responses were dramatically better in the combination treatment group during double-blind treatment, with cell counts returning to baseline in the zidovudine monotherapy group by week 24. With the addition of lamivudine at week 24, cell counts in the original monotherapy group then increased to levels comparable to those in the patients who were originally randomized to and continued to receive combination therapy. Counts in both groups remained above baseline after 56 weeks.

Identical effects on viral load were observed in the subgroup of patients assessed by plasma HIV RNA polymerase chain reaction (PCR) assay. The combination treatment patients exhibited a median 1.5 log drop in plasma HIV RNA level—a decrease markedly greater than that in the zidovudine monotherapy patients. When lamivudine was added to monotherapy at week 24, viral load persistently decreased until it was at a level similar to that in the original combination treatment patients by week 48, with both groups exhibiting a level approximately 1 log lower than baseline levels at that time. Dr Friedland noted that the decrease in viral load with combination treatment was impressive compared with decreases reported with other nucleoside analogue combinations.

In NUCB 3002, 223 patients with CD4+ cell counts of 100 to 400/µL who had received ≥24 weeks of prior zidovudine were randomized to double-blind treatment with zidovudine 200 mg tid alone or in combination with lamivudine 150 mg or 300 mg bid. After 24 weeks, open-label lamivudine was added in all zidovudine monotherapy patients. CD4+ cell counts rapidly dropped below baseline in the zidovudine monotherapy patients and remained above baseline for the 24 weeks of double-blind treatment in both combination treatment groups. With the addition of lamivudine in the initial zidovudine monotherapy group at 24 weeks, the CD4+ cell count in this group increased to above baseline levels and remained above baseline at week 48.

In NUCA 3002, 254 patients with CD4+ cell counts of 100 to 300/µL and ≥24 weeks of prior zidovudine treatment were randomized to double-blind treatment with zidovudine 200 mg tid plus lamivudine 150 mg or 300 mg bid or zalcitabine 0.75 mg tid. Mean actual changes in CD4+ cell count were greater in the two lamivudine combination arms than in the zidovudine plus zalcitabine arm, with counts remaining above baseline levels for at least 52 weeks in the former groups and remaining at or below baseline in the zidovudine plus zalcitabine group.

As an example of the type of safety data that are emerging from these trials, Dr Friedland presented frequencies of drug-related clinical adverse events in patients in study NUCA 3002, stating that the very minimal toxicity that has thus far been associated with lamivudine has consisted primarily of headache and nausea. A similar proportion of patients in the zidovudine monotherapy group (55%) and the two combination groups (55% and 56%) reported no drug-related events.

Clinical outcome data from lamivudine studies are not yet available and are awaited with considerable interest. Data on the use of the agent in combination with agents other than zidovudine currently are lacking. However, a number of trials of such combinations are in progress or design.

**NNRTIs**

The NNRTIs are a structurally diverse but functionally similar group of compounds that include TIBO derivatives, BHAP compounds (eg, etravirine, delavirdine), nevirapine, and pyridinone derivatives (eg, L-697,661), all of which work by binding directly to RT. The agents are potent inhibitors of HIV-1, including zidovudine-resistant isolates. Because they rapidly select for resistant virus in vitro and in vivo, combination therapy is the primary role envisioned for these compounds. However, study of nevirapine monotherapy has shown that some patients have a persistent virologic and immunologic response to the agent despite the development of mutations conferring high-level resistance, suggesting that the susceptibility level of resistant virus can be exceeded in some cases. The agents that have been clinically investigated have been generally well tolerated. The characteristic primary adverse reaction is rash, which typically occurs early during treatment and can be treated through.

As noted by Dr Friedland, the use of nevirapine and zidovudine in combination does not prevent the emergence of nevirapine resistance. Data on nevirapine resistance mutations in isolates from patients receiving monotherapy in ACTG 164 and combination therapy in ACTG 168 indicate that although resistance is not prevented, the distribution of mutations at the RT

| Table 4. Effect of Concomitant Therapy With Zidovudine on Nevirapine Resistance Mutations |
|---------------------------------|----------------|----------------|----------------|----------------|--------|--------|
| Percent of patients with isolates developing mutations at indicated RT residue | 103 | 106 | 108 | 181 | 188 | 190 |
| Nevirapine monotherapy, ACTG 164; n=24 | 33 | 0 | 8 | 79 | 8 | 17 |
| Nevirapine + zidovudine, ACTG 168; n=14 | 57 | 14 | 0 | 0 | 50 | 50 |

codons implicated in resistance is different under combination therapy (Table 4); for example, whereas the majority of monotherapy patients developed the characteristic codon 181 nevirapine resistance mutation, this mutation was not observed in isolates from the combination patients, with mutations at other codons being observed with increased frequency. These findings at once point out that the virus has an array of evolutionary options available to avoid susceptibility and that there may be an inherent constraint on the evolutionary pathways that can be taken. Exploitation of the latter feature in the clinical setting remains a matter for further study.

Another provocative phenomenon observed with nevirapine therapy is that, as noted above, a significant proportion of patients have a sustained antiviral response to higher-dose nevirapine despite the development of resistance. As presented by Dr. Pottage, Figure 2 shows changes in HIV p24 antigen levels in patients receiving nevirapine 200 mg/d or 400 mg/d; as can be seen, the decrease among patients receiving the higher dosage was persistent, indicating ongoing antiviral effect. As presented by Dr. Friedland, analysis of nevirapine plasma levels in patients receiving 400 mg/d who exhibited persistent response vs those who did not exhibit such response showed that trough levels were significantly greater in responding patients (Figure 3), suggesting that the susceptibility level of resistant virus can be overcome if sufficient blood-drug levels can be maintained; it is not yet known if it can be predicted which patients are likely to respond to nevirapine in this manner. It may be the case that similar phenomena occur with other antiretroviral agents.

Preliminary findings of ACTG 241, a phase II study of triple combination therapy including nevirapine vs double combination treatment, indicate superiority of the triple regimen with regard to virologic and immunologic markers. No clinical differences were observed, although the ability to detect a difference may have been beyond the scope of the study. In this study, patients with a CD4+ cell count <350/μL and ≥6 months of prior nucleoside analogue treatment were randomized to zidovudine 600 mg/d plus didanosine 400 mg/d with or without nevirapine 400 mg/d. The patients had a mean CD4+ cell count of 138/μL and a median duration of prior therapy of 25 months. According to Dr. Pottage, the triple combination was associated with a clear benefit in CD4+ cell count increase and decreases in PBMC viral titer and plasma viral RNA levels. Further studies of the potential clinical benefit of combination treatment including nevirapine are under way.

Delavirdine (a BHAP compound) is another NNRTI with significant promise that is currently being extensively investigated in clinical trials. As with other NNRTIs, resistance to BHAP compounds is rapidly selected for, with resistance in vitro being observed after three to five passages. In early studies, the agent has been well tolerated at doses up to 400 mg tid. Rash has been observed in 27% to 38% of patients, but patients were successfully rechallenged or treated through the effect in all but one case. The agent undergoes hepatic metabolism and exhibits increased clearance in the presence of rifampin and rifabutin. Increased liver function tests have been observed in combination therapy recipients. Early findings with combination therapy including delavirdine have indicated that sustained improvements in immunologic and virologic markers are achieved. Studies of delavirdine monotherapy and combination therapy are ongoing. Studies currently open for enrollment include ACTG 260 and ACTG 261.

In summarizing the current status of NNRTIs, Dr. Friedland observed that: (1) three agents (nevirapine, delavirdine, and loviride) are in the advanced stages of clinical development; (2) the pharmacologic and safety profiles of these classes of agent are favorable; (3) although altered drug susceptibility occurs rapidly, improvements in virologic and immunologic markers have been demonstrated with monotherapy and combination therapy; and (4) larger clinical trials will determine whether these agents provide sufficient benefit in terms of viral load reduction and clinical outcome to be clinically useful.

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John C. Pottage, Jr., is Associate Professor of Internal Medicine, Section of Infectious Disease, at Rush Medical College, Chicago, Illinois.
PATHOGENESIS OF HIV INFECTION

The pathogenesis of HIV infection was discussed at the New York meetings by David D. Ho, MD, from the Aaron Diamond AIDS Research Center and New York University School of Medicine, New York, New York. Dr Ho's presentation focused on recent studies by his group on the dynamics of HIV and CD4+ cell turnover in vivo and featured discussion of the implications of their findings for treatment practices.

Observational studies of HIV-1 pathogenesis have indicated that increased viral load is correlated with CD4+ lymphocyte depletion and disease progression. However, these studies have provided little information on the kinetics of HIV and CD4+ cell turnover. Dr Ho and colleagues recently performed interventional studies in which the effects of an antiretroviral agent in perturbing the balance between virus production and clearance were utilized to permit assessment of such kinetics in vivo.

HIV Kinetics

Although it is known that disease progression is associated with increased viral load, viral load remains relatively stable over the short term in infected individuals, indicating a steady state relationship between virus production and virus clearance (Figure 1). In a phase I/II study of a potent protease inhibitor (ABT-538, ritonavir) in 20 patients (mean CD4+ cell count of 180/μL), viral load and CD4+ cell count responses were closely followed, with the intention of deriving kinetics data on the pretreatment steady state by observing the effects of “turning off” viral production with treatment. Figure 2A provides representative data from three subjects with regard to plasma HIV RNA response to initiation of treatment, with a similar response being observed in all patients treated: (1) prior to treatment, there is relative stability of RNA levels; and (2) there is a rapid decline in viral load over the first 2 weeks of treatment. Particularly during the first 10 days of treatment, the data points exhibit a linear decline on the log plot, indicating that the viral level is decreasing exponentially. Measurement of the slope of the line best fitting these data points allows direct calculation of the clearance or decay half-life of the viral population. For the subjects represented in Figure 2A, these half-life values were 3.3, 2.2, and 1.5 days. The slopes of the exponential decay in viral load for all 20 patients are shown in Figure 2B, with the magnitude of the decay also being represented by the length of each line; it can be seen that responses were similar among all subjects, with the decrease being equivalent to an approximately 2-log drop in viral load.

For each patient, the slope was derived and the decay half-life calculated. With this information, the minimum rates of viral production and viral clearance at steady state could be calculated, based on volume of distribution in accordance with patient weight and the pretreatment steady state viral load. Table 1 shows the mean and range of values for all 20 patients. The mean slope of -0.34 indicates that approximately 30% of the virus in the blood is turning over each day, with this rate being equivalent to a half-life of approximately 2 days. The mean minimum


TABLE 1. VIRAL KINETICS IN 20 SUBJECTS

<table>
<thead>
<tr>
<th>Baseline values</th>
<th>Kinetics of HIV-1 turnover</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CD4+ count (cells/μL)</td>
</tr>
<tr>
<td>Range</td>
<td>36 – 490</td>
</tr>
<tr>
<td>Mean</td>
<td>180 ± 46</td>
</tr>
</tbody>
</table>

production and clearance of virus calculated on the basis of these figures is 0.68 billion viral particles per day at steady state. As noted by Dr Ho, although patients with CD4+ cell counts >500/μL have not yet been studied in this manner, it is suspected that the viral dynamics in such patients are similar, although the numbers of particles involved might be quantitatively smaller.

Wei and colleagues at the University of Alabama at Birmingham have performed similar studies and have arrived at similar figures for half-life and production and clearance. Dr Ho stressed that the figures arrived at for production and clearance must be considered minimum estimates, since their calculation is based on particular assumptions. First, the viral decay is actually a reflection of two parameters—clearance of viral particles from the circulation and death of productively infected CD4+ lymphocytes. The calculations take into account only the former parameter and further assume that virus production is completely shut off immediately upon initiation of drug administration. Thus the actual production and clearance rates are higher than the calculated values.

Residual Plasma Viremia

An important characteristic of the decrease in viral load with institution of the anti-HIV intervention is that there is a floor that is reached in reduction; as can be seen from Figure 2B, the decreases typically are from 10^5 to 10^6 to approximately 10^3 RNA copies/mL, with the residual viremia representing a level of approximately 0.1% to 1.0% of the initial steady state viral load. Dr Ho stated that there are a number of potential explanations for this residual viremia (Table 2). (1) There may be inadequate drug penetration to some sites where actively infected cells are sequestered. (2) There may be drug-resistant virus present at or shortly after the initiation of treatment. (3) There may be a population of long-lived cells that continue to produce virus; although such virus will be noninfectious, they would be accounted for in the HIV RNA assay. (4) There may be a pool of latently infected cells that gradually enter the population of cells that are actively producing virus, a phenomenon that would go unperturbed by the intervention with the protease inhibitor. Further investigation will be necessary to identify the source or sources of the residual viremia.

An important implication of the residual viremia is that, given its low level, it can be inferred that the vast majority of virus present in the plasma comes from recently infected cells. That is, the approximately 99% of the plasma viral population—that proportion whose production is turned off by the intervention—is supplied by cells infected only a few days prior and is constantly turning over. As noted, the residual proportion may be supplied by activation from latent to producer cells or generated by chronically infected productive cells (eg, macrophages). The residual viremia pool must be dealt with, since it is capable of re-igniting the high-level, continuous HIV-1 replication when an effective antiretroviral agent is withdrawn.

Viral Clearance and Disease Stage

Numerous published data demonstrate that more advanced disease is associated with higher viral load. Nevertheless, as can be seen from Figure 2B, the slopes of viral clearance in patients with higher viral load are essentially equivalent to those in patients with lower viral load at baseline. This study performed by Dr Ho and colleagues indicates that rate of viral clearance is not substantially affected by disease status. The same point is made by analysis of viral clearance rate by initial CD4+ cell count in these patients, in which no obvious correlation is evident (Figure 3). Thus it can be concluded that viral load is largely not a function of viral clearance, since clearance efficiency varies little.

Table 2. Import of Residual Viremia (≈1%)  

<table>
<thead>
<tr>
<th>Potential explanations</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate drug penetration</td>
<td>It can be inferred from finding of residual viremia that nearly all of the plasma virus must come from recently infected cells</td>
</tr>
<tr>
<td>Drug-resistant virus</td>
<td></td>
</tr>
<tr>
<td>Long-lived, virus-producing cell population</td>
<td></td>
</tr>
<tr>
<td>Gradual activation of latently infected cells</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3. Analysis of viral clearance rate by baseline CD4+ cell count in subjects receiving ABT-338. Data indicate absence of correlation. Adapted from Ho DD et al. Nature 1995.
among individuals and since individuals can differ in viral load by several orders of magnitude. It therefore seems that viral load is primarily a function of viral production.

**Implications of High Turnover and Mutation Rates**

As related by Dr Ho, the high replication rate of the virus has important implications for treatment. Based on the kinetics studies, it can be estimated that the viral population undergoes between 3000 and 5000 replication cycles over the course of 10 years, producing a minimum of $10^{12}$ virions. According to Dr Ho, given the assumptions in the kinetics analysis that render the figures minimum estimates, the number of virions produced is probably actually closer to $10^{13}$. Retroviruses, including HIV, have been shown to have a mutation rate of approximately $10^{-4}$. As stated by Dr Ho, the combination of having this many rounds of replication and this high a transcription error rate results in "too many variants!!"

In brief, the enormous quantity and great genetic diversity achieved by the virus in vivo can outstrip the ability of the immune system to recognize and respond to the virus, permitting resistant mutants to emerge and, ultimately, gain predominance. This suggests that the simultaneous use of multiple potent antiretroviral agents may constitute a reasonable treatment strategy, since it would require the viral population to acquire multiple and perhaps disadvantageous mutations in the attempt to avoid susceptibility.

**CD4+ Lymphocyte Kinetics in HIV Infection**

Dr Ho also provided data on CD4+ cell kinetics in the subjects in the intervention study. In the study, there was a reciprocal relationship between change in viral load and CD4+ cell count with initiation of ABT-538 treatment. Derivation of the slopes of the CD4+ cell increases permitted calculation of the doubling time of the CD4+ cell population. It was calculated that approximately 5% of the CD4+ cells are being regenerated per day, indicating a destruction rate of approximately 5% per day during steady state (Table 3). The 5% figure is equivalent to a daily turnover of approximately 35 million cells in the bloodstream. Since the bloodstream accounts for approximately 2% of the total lymphoid population, it can be estimated that the total population minimum production and destruction rate is approximately 1.8 billion CD4+ cells per day. When the individual rates of CD4+ cell repopulation were plotted against initial CD4+ cell counts for the 20 subjects, an inverse correlation was found, with those subjects with the lowest counts exhibiting the greatest production rates (Figure 4).

This finding was somewhat surprising, given the expectation based on prior literature that patients with more advanced illness would have the lowest regenerative capacity. The implication is that the body is trying extremely hard in late-stage disease to counter the greater destruction rates associated with the greater quantity of actively replicating virus. The regenerative processes may indeed be maximally turned on in late-stage disease.

Using the analogy of a faucet and basin, Dr Ho likened the water level in the basin to the CD4+ cell count, the faucet to cell replenishment, and the drain to viral destruction of cells. In the analogy, the basin drains just slightly faster than replenishment occurs, with the faucet turned full on in late-stage disease. Dr Ho maintained that the major objective of treatment should be to

---

**Table 3. Kinetics of CD4+ Lymphocyte Turnover in 20 Subjects**

<table>
<thead>
<tr>
<th>Slope</th>
<th>Minimum production and destruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>Blood (cells/d $\times 10^5$)</td>
</tr>
<tr>
<td>0.004 – 0.088</td>
<td>4.3 – 108.00</td>
</tr>
<tr>
<td>0.004 – 0.088 (0.5 – 25.7)</td>
<td>(2.7 – 157.0)</td>
</tr>
<tr>
<td>Mean</td>
<td>0.047</td>
</tr>
<tr>
<td>Mean</td>
<td>(8.6)</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td></td>
</tr>
</tbody>
</table>
plug the drain rather than solely attempt to increase the amount of water going into the basin—eg, through immune-based therapies designed to boost CD4+ cell production. He suggested that it is difficult to imagine how CD4+ cell production rate could be augmented beyond that observed in late-stage disease. He noted, however, that the functional capacity of regenerating CD4+ lymphocytes may be limited; thus, efforts to restore immune function are still necessary.

**Implications for Pathogenesis and Treatment**

In summarizing the findings of these kinetics studies (Table 4), Dr Ho stated that the CD4+ lymphocyte depletion seen in AIDS is primarily a consequence of the destruction of these cells induced by HIV, not a lack of their production. At least two important implications for pathogenesis of HIV disease can be drawn from the findings: (1) continuous, high-level replication of HIV is the engine that drives the pathogenesis of infection; and (2) the CD4+ lymphocyte replenishment process is highly stressed, especially in later stages.

The implications for treatment are several fold. First, the primary effort must be to attack the virus. As noted by Dr Ho, this does not mean that treatment aimed at reconstitution of the immune system will not have additional important applications. Secondly, since rapid turnover of HIV results in increasing viral diversity with time, aggressive treatment should be initiated early if dramatic clinical impact is desired. Thirdly, at least with re-

<table>
<thead>
<tr>
<th>Table 4. Kinetics Studies Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CD4+ lymphocyte depletion seen in AIDS is primarily a consequence of the destruction of these cells induced by HIV-1, not a lack of their production</td>
</tr>
<tr>
<td>• Pathogenesis implications</td>
</tr>
<tr>
<td>(1) Continuous, high-level replication of HIV is the engine that drives the pathogenesis of infection</td>
</tr>
<tr>
<td>(2) CD4+ lymphocyte replenishment process is highly stressed (working overtime), especially in later stages</td>
</tr>
<tr>
<td>• Treatment implications</td>
</tr>
<tr>
<td>(1) Our primary effort must be to attack the virus</td>
</tr>
<tr>
<td>(2) Because rapid turnover of HIV results in increasing viral diversity with time, aggressive treatment should be initiated early if we wish to achieve a dramatic clinical impact</td>
</tr>
<tr>
<td>(3) Rapid turnover of plasma virus suggests that monitoring must be early and frequent</td>
</tr>
</tbody>
</table>

David D. Ho is Director of the Aaron Diamond AIDS Research Center and Professor of Medicine and Microbiology at New York University School of Medicine, New York, New York.
PROTEASE INHIBITORS

Recent clinical findings with candidate protease inhibitors were discussed at the New York meeting by Michael S. Saag, MD, from the University of Alabama at Birmingham.

The HIV-1 protease performs a critical function in the life cycle of the virus, cleaving polyprotein precursors into enzymes (such as integrase, reverse transcriptase, RNase H, and protease itself) and structural proteins (such as the nucleocapsid, capsid, and matrix) that make up the central viral core. The process begins during the final stages of viral assembly and continues as the virion buds through the host cell membrane. A number of pharmaceutical companies have designed and developed molecules that fit into and bind in the cleavage site of the protease enzyme to inhibit its function in producing the core components. HIV-1 cell lines exposed in vitro to protease inhibitors produce noninfectious virions characterized by the absence of the dense central viral core (Figure 1). Problems with protease inhibitor development have included increasing the water solubility of the molecules to ensure and enhance oral bioavailability and an expensive, demanding, and laborious production process.

Saquinavir (Ro31-8959)

Four protease inhibitors have undergone evaluation in HIV-infected subjects. Saquinavir (initially Ro31-8959), the most extensively evaluated, is now undergoing phase III testing. Initial evaluation of the compound consisted of three European 16-week phase I studies in which the compound was found to be well-tolerated and to have minimal side effects. In two monotherapy studies, saquinavir at dosages of 75 to 1800 mg/d was found to be associated with dose-related CD4+ cell responses. In one combination study in zidovudine-naïve patients, the combination of saquinavir and zidovudine was associated with greater CD4+ cell response than either saquinavir or zidovudine monotherapy.

Subsequently, saquinavir was evaluated in ACTG 229, the largest trial of a protease inhibitor in humans to be completed to date. Patients with CD4+ cell counts of 50 to 300/µL and extensive prior zidovudine treatment (median >24 months) were randomized to receive saquinavir 600 mg tid plus zidovudine 200 mg tid, zidovudine plus zalcitabine 0.75 mg tid, or a combination of the three agents. After 24 weeks of treatment, the triple-drug regimen was associated with greater reductions in viral load and a greater and more enduring CD4+ cell response. Figure 2 shows the change in mean CD4+ cell count over 24 weeks. CD4+ cell counts increased by at least 50/µL in 39% of the triple combina-

Figure 1. Top. HIV (HIV-IIB) budding from infected CEM cells show presence of dense viral core. Bottom. Virions budding from cells after exposure to 100 nM of protease inhibitor saquinavir are characterized by absence of core components.

Four protease inhibitors have undergone evaluation in HIV-infected subjects, and one is now undergoing phase III testing.
observed, although levels generally return to baseline with continuation of monotherapy for >12 to 24 weeks. Nevertheless, sustained elevations of CD4+ cell count have been observed to persist beyond 24 weeks. As with other protease inhibitors evaluated, viral isolates exhibit reduced susceptibility to MK639 after relatively short-term treatment. Figure 3 shows the HIV p24 antigen response and plasma HIV RNA response to MK639 administration in four patients.

Although HIV p24 antigen remains suppressed for the entire 12 weeks shown, viral RNA levels begin to return to baseline level. It has been noted that HIV p24 antibody levels increase dramatically in such patients. It is believed that an altered form of HIV p24 is produced under protease inhibitor treatment and that new HIV p24 antibodies produced in response mask the presence of HIV p24 antigen in the circulation as detected by p24 ELISA assay. Thus, whereas measurement of HIV p24 antigen level with current assays provides the impression of maintained suppression of replication, the viral RNA assays indicate a gradual return in replication. There have been cases of dramatic increases in CD4+ cell count under treatment with this protease inhibitor. In one case, a patient’s count rose from 7/μL to 215/μL and the CD4+ cell percentage increased from 1% to 16%. After more than 1.5 years of treatment with the agent, the patient’s count is at 30 to 40/μL. Results of phase II trials with this agent should be available in 1995.

ABT-538

Preliminary results of phase I trials with ABT-538 dosed at 200 to 300 mg q6h or q8h in the United States and 300 to 600 mg bid in Europe and Australia have documented 1 to 3 log decreases in viral load and 35% to 95% increases in CD4+ cell counts during 12 to 16 weeks of dosing. According to Dr Saag, the gradual return of viral replication after 6 to 12 months of treatment also has been observed with this agent. The formulation of the agent has a characteristic poorly tolerated taste, but few adverse events have been observed thus far. Dramatic CD4+ cell count elevations have also been reported with ABT-538—one Australian patient was reported to have an increase from approximately 70/μL to 550/μL.

SC-52151

As related by Dr Saag, some of the difficulties with development of protease inhibitors as therapeutic agents have been pointed out from the experience with SC-52151. This agent demonstrated potent in vitro activity, and was evaluated in a rapidly accrued phase I study of two formulations. This study (ACTG 282) demonstrated no measurable effects on HIV RNA levels, HIV p24 antigen levels, or CD4+ cell counts despite the achievement of adequate serum drug levels. Subsequent study revealed that a serum protein, alpha-1 acid glycoprotein, tightly bound the inhibitor and dramatically reduced the intracellular uptake of the compound. The manufacturer has halted further development of the compound.

Protease Inhibitor Cross-Resistance

Although it was initially believed that cross-resistance among different protease inhibitors was rare or unlikely, recent
Table 1. **Protease-specific Amino Acid Substitutions (Serum Viral RNA) in a Patient Receiving MK639 Monotherapy**

<table>
<thead>
<tr>
<th>Week</th>
<th>Protease amino acid substitutions</th>
<th>IC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>L10V, T12I, G16E, R57K, I64V</td>
<td>50</td>
</tr>
<tr>
<td>12</td>
<td>L10R, M461, R57K, I64V</td>
<td>100</td>
</tr>
<tr>
<td>24</td>
<td>L10R, M461, (L63P), (I64V), V82T</td>
<td>400/800</td>
</tr>
</tbody>
</table>

Parentheses indicate substitutions that occur less frequently. IC₅₀ = 95% inhibitory concentration.

Recent data have shown that decreases in susceptibility to most of the available protease inhibitors will develop with treatment of sufficient duration; these findings remain to be validated, however.

Investigation has shown that with treatment of sufficient duration, decreases in susceptibility to most of the available inhibitors are observed. However, the decrease in susceptibility observed among the inhibitors was not uniform and the findings remain to be validated. Table 1 shows an example of the amino acid substitutions and associated decreases in susceptibility over time in isolates from a patient receiving protease inhibitor monotherapy. As stated by Dr Saag, what occurs in terms of resistance when combination treatment involving these agents is begun early in infection remains to be determined. He noted the possibility that use of combinations of protease inhibitors might forestall or prevent selection for some resistant mutants through interaction of resistance mutations. Ongoing and future studies will better define the potency, durability, and clinical utility of the protease inhibitors in combination with existing nucleoside analogues, NNRTIs, and with each other.

Michael S. Saag is Associate Professor of Medicine and Director of the AIDS Outpatient Clinic at the University of Alabama at Birmingham.
PEDIATRIC HIV INFECTION

New developments in pediatric HIV infection were discussed at the Chicago meeting by Ellen Gould Chadwick, MD, from Northwestern University Medical School and The Children's Memorial Hospital, Chicago, Illinois.

ACTG 152: Preliminary Findings

As related by Dr Chadwick, an interim analysis of a large comparative trial (ACTG 152) in children with symptomatic infection and little or no prior experience with antiretroviral treatment has indicated that either didanosine monotherapy or didanosine-zidovudine combination therapy is associated with significantly delayed clinical progression compared with zidovudine monotherapy. In ACTG 152, patients aged 3 months to 18 years with mild to severe symptomatic disease, low age-adjusted CD4+ cell counts, and less than 6 weeks of prior antiretroviral therapy were randomized to receive zidovudine 180 mg/m² q6h, didanosine 120 mg/m² q12h, or zidovudine 120 mg/m² q6h plus didanosine 90 mg/m² q12h. The primary study end point was defined as time to death or clinical progression, with the latter defined as growth velocity change, neuropsychological deterioration, or at least 2 new or recurrent opportunistic infections.

The fourth scheduled interim analysis involved 831 evaluable patients with a median follow-up of 24 months. At the time of this analysis, 9% of patients had died, 60% remained on initial randomized treatment, 23% had been permanently discontinued from original treatment, and 21% had reached a primary end point. One of the treatment arms—either the didanosine monotherapy arm or the didanosine-zidovudine combination arm—was found to exhibit a significantly longer time to disease progression (P = 0.0058) and a longer time to development of hematologic toxicity (P = 0.0003) and liver or pancreatic toxicity (P = 0.034) compared with the zidovudine monotherapy arm. There was no difference in survival between the zidovudine group and the group exhibiting delayed disease progression (P = 0.28). Since the study continues with blinded treatment in the other treatment arms, it is not yet known which treatment was associated with this comparative benefit. On the basis of these findings, it was recommended that the zidovudine monotherapy arm be discontinued, with the patients being offered alternative treatment. Continuation of the study will determine whether there are differences between didanosine monotherapy and combination therapy.

An Approach to Treatment

It should be remembered that whereas the findings of the study indicate that either didanosine alone or in combination with zidovudine is superior to zidovudine alone in delaying clinical progression, the data do not allow generalizations regarding the efficacy of zidovudine in preventing maternal-fetal/neonatal vertical transmission, the treatment of asymptomatic infants or children, or the treatment of adults.

In stating that there remains no consensus regarding how to use antiretrovirals in the pediatric population at this time, Dr Chadwick noted that many physicians are reluctant to abandon initial use of zidovudine in children in light of the study findings. Since earlier noncomparative data showed that in addition to being very well tolerated, zidovudine treatment was associated with often striking improvements in energy, weight gain, linear growth, and neurocognitive function.

In outlining a treatment strategy based on currently available experience, Dr Chadwick presented the current approach in her own practice, cautioning that the approach is eminently subject to change based on further information. At present, the approach to the asymptomatic patient with moderate immune suppression is to (1) treat with zidovudine monotherapy, (2) monitor for laboratory evidence of zidovudine resistance, and (3) change to another agent as resistance is documented or disease progression occurs. An additional option is to rotate agents in patients without signs of resistance or progression. In symptomatic patients or asymptomatic patients with severe immune suppression, didanosine monotherapy or combination treatment with zidovudine plus didanosine or zalcitabine would be used. Current recommendations suggest that asymptomatic children who do not have immunosuppression should not be treated. However, these recommendations were made prior to findings regarding the rapid turnover of virus in vivo and noted that, given the implication that treatment should be initiated early to keep viral load suppressed, new recommendations regarding treatment in such children would likely be forthcoming.

PCP Prophylaxis

Pneumocystis carinii pneumonia (PCP) remains the most common opportunistic infection and cause of death in pediatric patients. According to Centers for Disease Control and Prevention (CDC) data for 1993, PCP was the most common AIDS-defining diagnosis in children with perinatally acquired infection, accounting for approximately 30% of cases. As shown in Figure 1, the highest incidence of PCP in children with perinatally acquired infection is between 3 and 5 months of age. Many of these infants develop PCP before a diagnosis of HIV infection is made or suspected. The mean survival of patients developing
PCP at this age is approximately 1 month with many dying within a few days of presentation despite maximal antibiotic therapy and ventilatory support. Based on earlier data indicating that CD4+ cell counts in children were approximately twice those in normal adults, the CDC issued guidelines in 1991 that called for initiation of PCP prophylaxis using a CD4+ cell count threshold of 1500/μL, which was believed to predict which infants were at highest risk of developing disease. These guidelines failed to significantly reduce the incidence of PCP in the age group with the highest incidence.

One reason for this failure is that infants with HIV infection are probably not being identified early enough to benefit from prophylaxis. In one CDC survey, approximately two thirds of 300 infants had not received prophylaxis prior to PCP onset. In another survey, 59% of infants had not been assessed for HIV infection at more than 30 days prior to onset of PCP. An additional reason for the failure of the guidelines appears to be that the CD4+ cell count threshold of 1500/μL specified in the initial guidelines fails to identify a substantial proportion of patients at high risk for PCP. As shown in Table 1, 22% of children aged 0 to 5 months at the time of PCP onset had counts >1500/μL. In addition, the initial guidelines recommended assessment of cell count every 3 months in children being followed. However, as shown in data presented by Dr Chadwick, CD4+ cell counts in infants could precipitously drop to below the threshold level in a much shorter duration.

As a result of the failure of the prior recommendations, new guidelines for PCP prophylaxis in HIV infected or HIV-exposed children have been formulated; these are shown in Table 2. Under these guidelines, no prophylaxis is recommended for children aged up to 4 to 6 weeks, in whom the risk of PCP is exceedingly low. Sulfis-containing drugs are avoided in this age group due to the competitive binding of bilirubin with albumin that can cause jaundice and kernicterus and also, due to the potential for additive toxicity with zidovudine in those infants receiving zidovudine in regimens for prevention of perinatal transmission. From 4 to 6 weeks to 4 months of age, all children known to be HIV infected or who were born to a mother with HIV infection should receive prophylaxis. Prophylaxis should continue until 1 year of age unless absence of HIV infection is documented by at least two negative cultures or PCR assays. Prophylaxis should be maintained or instituted in children aged 1 to 5 years if the CD4+ cell count is lower than 500/μL or the CD4+ cell percentage is less than 15% and for children aged 1 to 2 years in whom the cell count fell below 750/μL in the first year of life. In this age group and in older children, prophylaxis should also be considered if CD4+ cell count is rapidly declining. For children aged 6 to 12 years, prophylaxis is recommended if the CD4+ cell count is less than 200/μL or the proportion is less than 15%. The recom-

**Table 1. Infants With Pneumocystis carinii by Age and CD4+ Cell Count Within 1 Month of Pneumonia**

<table>
<thead>
<tr>
<th>CD4+ cell count (cells/μL)</th>
<th>Age at PCP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–5 months</td>
</tr>
<tr>
<td>≥1500</td>
<td>20 (22%)</td>
</tr>
<tr>
<td>750–1499</td>
<td>24 (26%)</td>
</tr>
<tr>
<td>500–749</td>
<td>9 (10%)</td>
</tr>
<tr>
<td>200–499</td>
<td>19 (21%)</td>
</tr>
<tr>
<td>&lt;200</td>
<td>19 (21%)</td>
</tr>
<tr>
<td>Total</td>
<td>91 (100%)</td>
</tr>
</tbody>
</table>

**Figure 1. AIDS-defining condition by age among AIDS patients aged <2 years who acquired infection perinatally. US data through December 1993. Data are from the Centers for Disease Control and Prevention.**

**Table 2. Recommended Pneumocystis carinii Pneumonia Prophylaxis for HIV-infected and HIV-exposed Children**

<table>
<thead>
<tr>
<th>Age</th>
<th>PCP prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 4–6 weeks</td>
<td>None</td>
</tr>
<tr>
<td>4–6 weeks to 4 months</td>
<td>All</td>
</tr>
<tr>
<td>4–12 months</td>
<td></td>
</tr>
<tr>
<td>HIV-uninfected</td>
<td>None</td>
</tr>
<tr>
<td>HIV-infected/indeterminate</td>
<td>All</td>
</tr>
<tr>
<td>1–5 years</td>
<td>If CD4+ &lt;500/μL or &lt;15%²³</td>
</tr>
<tr>
<td>6–12 years</td>
<td>If CD4+ &lt;200/μL or &lt;15%³</td>
</tr>
</tbody>
</table>

¹ ≥2 negative culture/PCR, both at ≥1 month and one at ≥4 months.
² Children aged 1 to 2 years should continue prophylaxis if CD4+ cell count was <750/μL in first year of life.
³ Prophylaxis also considered for children with rapidly declining CD4+ cell counts/Category C conditions.
TABLE 3. PROPHYLAXIS REGIMEN FOR PNEUMOCYSTIS CARINII PNEUMONIA IN CHILDREN

- Recommended regimen
  
  TMP-SMX (for children >1 month old)
  - TMP 150 mg/m²/d plus SMX 750 mg/m²/d orally
    in 2 divided doses 3 d/wk on consecutive days
    (eg, Monday, Tuesday, Wednesday)
  
  TMP-SMX alternate schedules
  - Single daily dose 3 d/wk on consecutive days
    (eg, Monday, Tuesday, Wednesday)
  - 2 divided doses 7 d/wk
  - 2 divided doses 3 d/wk on alternate days
    (eg, Monday, Wednesday, Friday)

- Alternative agents
  
  Dapsone 2 mg/kg qd orally
  Pentamidine
  - Aerosolized, for children aged >5 years: 300 mg
    monthly
  - IV: 4 mg/kg every 2–4 weeks
  Atovaquone: experimental

TMP indicates trimethoprim; SMX indicates sulfamethoxazole.

mended prophylactic regimen consists of trimethoprim/ sulfamethoxazole (TMP/SMX) in the standard or alternate regimens shown in Table 3; alternative agents include dapsone in a recently revised regimen of 2 mg/kg/d, aerosolized pentamidine (children older than 5 years) or IV pentamidine, and atovaquone. The single most important feature of successful prophylaxis remains the early identification of infants at risk for HIV infection.

Rapid and Slow Progression in Perinatally Acquired HIV Infection

It was widely accepted several years ago that children with perinatally acquired HIV infection developed rapidly progressive disease, with an estimated 80% mortality by 3 years of age. However, with further study, it has become clear that the presentation of disease is at least bimodal. Approximately 30% of children acquiring the disease perinatally are rapid progressors, with infection course characterized by early onset of moderate-to-severe symptoms and death often occurring by 3 years of age despite intervention. Rapid progression may correlate with intratuerne transmission. Many of these children are found to be culture- or PCR-positive at birth, suggesting that infection may have been established in the context of an immune system less able to curtail viral replication due to its relative immaturity. Approximately 70% of children appear to be slow progressors, being asymptomatic and without significant physical findings for several years and having a life expectancy of greater than 5 years. Slow progression may correlate with intrapartum transmission, with such children tending to have negative PCR assay and cul-

ture findings at birth. Figure 2 shows representative survival curves for children with symptoms during the first year of life and those with symptoms only after 1 year of age. It can be seen that approximately 50% of children with diagnosis within the first year have died by 2 years of age, with more than 50% of those with later onset of symptoms remaining alive after 5 years.

Epidemiology of Adolescent AIDS Cases

Dr Chadwick also presented epidemiologic data on adolescent HIV disease. Recent data indicate that adolescents comprise the second most rapidly growing population of newly infected Americans, that 15% of all adult AIDS cases acquired HIV infection during adolescence (assuming 10 years of infection prior to AIDS diagnosis), and that 25% of all patients acquiring infection through heterosexual contact were infected as teenagers. Figures for 1991 indicate that both black and Hispanic adolescents are disproportionately represented among AIDS cases, with the former accounting for 16% of the adolescent population and 36% of adolescent AIDS cases and the latter accounting for 10% of the adolescent population and 21% of adolescent AIDS cases (Figure 3). Updated figures indicate that black teenagers account for 39% of adolescent AIDS cases; 1992 estimates put the highest AIDS rate among black female adolescents, with a rate of 2.6 cases per 100,000 population.

CDC data from 1992 on exposure categories for adolescents and young adults by gender are shown in Table 4. Among females, the most frequently identified route of transmission is heterosexual contact, accounting for nearly half of all AIDS cases. According to Dr Chadwick, the actual proportion of cases attri-
utable to such transmission is higher, since most of the cases attributed to undetermined exposure are likely to be due to heterosexual contact. For males, the most common exposure category among young teenagers is contaminated cloting factor; homosexual contact is the second most common exposure category in the younger teenagers and is by far the most common exposure category among older teenagers.

Sexual activity is the primary risk factor for HIV infection among adolescents, with there being an increasingly younger age of first intercourse and very inconsistent condom use in this age group. Adolescents often have sexual encounters with older partners, who currently have a much greater prevalence of infection. Adolescents have the highest incidence of other sexually transmitted diseases, which are associated with more effective transmission of HIV. Other risk factors include drug-related behaviors such as sharing of IV drug “works” and a high frequency of unprotected sex because of impaired judgment—behavior particularly associated with the cocaine and alcohol use that is highly prevalent in the adolescent population. Runaways are at particularly high risk of infection, due to resorting to street prostitution for survival and the gravitation toward coastal cities with high prevalence rates of HIV infection.

Finally, Dr Chadwick emphasized that many of the issues of HIV infection and AIDS in adolescents have yet to be appropriately addressed. As a start, improved access to care for HIV-infected teenagers must be developed and new and creative approaches to educating adolescents about HIV disease must be devised and implemented. Although trained educators are probably the most valuable resource for HIV disease prevention efforts among teenagers, physicians have a unique opportunity to implement education efforts in the office setting.

Table 4. AIDS Cases in Female and Male Adolescents and Young Adults in the United States, by Exposure Category*

<table>
<thead>
<tr>
<th>Exposure category</th>
<th>13–19 years</th>
<th>20–24 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injecting drug use</td>
<td>72 (26)</td>
<td>659 (37)</td>
</tr>
<tr>
<td>Hemophilia/coagulation disorder</td>
<td>4 (1)</td>
<td>5 (&lt;1)</td>
</tr>
<tr>
<td>Heterosexual contact</td>
<td>131 (46)</td>
<td>872 (49)</td>
</tr>
<tr>
<td>Receipt of blood transfusion, blood components, or tissue</td>
<td>29 (11)</td>
<td>63 (4)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>39 (14)</td>
<td>163 (9)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>275 (100)</td>
<td>1762 (100)</td>
</tr>
</tbody>
</table>

| **Males**                                   |             |             |
| Men who have sex with men                   | 228 (34)    | 5141 (66)   |
| Injecting drug use                          | 50 (7)      | 986 (13)    |
| Men who have sex with men and inject drugs  | 37 (6)      | 833 (11)    |
| Hemophilia/coagulation disorder             | 278 (41)    | 242 (3)     |
| Heterosexual contact                        | 19 (3)      | 262 (3)     |
| Receipt of blood transfusion, blood components, or tissue | 28 (4)  | 66 (<1)     |
| Undetermined                                | 31 (5)      | 290 (4)     |
| **TOTAL**                                   | 671 (100)   | 7820 (100)  |

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