41st Interscience Conference on Antimicrobial Agents and Chemotherapy
Day 1 - December 16, 2001

The Global AIDS Epidemic: The Highs and the Lows

William A. O'Brien, MD, MS

Chicago, Sunday, December 16, 2001 -- The keynote session presented on the first day of the delayed 41st ICAAC once again focused on HIV/AIDS, as it has for most ICAAC opening sessions in the last decade. The meeting was postponed from late September because of the terrorist attacks, and the rescheduling moved the meeting to the 20th anniversary of the first reports of AIDS in a peer-reviewed journal in December 1981.[1-3] This session highlighted both the greatest disappointment of the epidemic, which is the devastation of AIDS in Africa, and the most encouraging and promising aspects of treatment, which is the pending emergence of a new class of drugs -- the entry inhibitors -- and the dramatic improvement in control of AIDS-related opportunistic diseases.

In the first presentation, Dr. Hoosen Coovadia[4] from the University of Natal Medical School in South Africa (winner of numerous awards for his efforts to treat AIDS in the poor regions of South Africa most affected by HIV), reviewed the AIDS epidemic in Africa and particularly the problems confronting South Africa. When thinking about the AIDS epidemic in sub-Saharan Africa it is hard not to be preoccupied by the grand scale of the devastation HIV has wrought, but Dr. Coovadia conveyed that behind each of the millions of cases reported in epidemiologic studies, there is a face, a person, a family, and a community. This is a disease unlike any other: one that is pervasive, affecting every institution and every sector of society, and arising out of expression of love and the creation of a family.

Dr. Coovadia began by reporting the latest global AIDS statistics, released by UNAIDS in early December 2001 (Table).[5]

Table Latest UNAIDS Estimates of the Global Impact of HIV/AIDS

Group	Estimated Numbers of Cases			
	Overall	Adults	Women	Children <15yo
AIDS	40 million	37.2 million	17.6 million	2.7 million
Infected in 2001	5 million	4.3 million	1.8 million	800,000
AIDS deaths	3 million	2.4 million	1.1 million	580,000

The majority of the cases are in sub-Saharan Africa, where currently 1 in 10 adults is

infected with HIV, rising to as high as 1 in 3 in the regions with the highest prevalence. The average life expectancy has declined to 40 years, after having increased to 67 years in South Africa and other more developed African countries before AIDS emerged.

In describing the impact of the epidemic, Dr. Coovadia talked about the disintegration of education, agriculture, industry, and family life. For example, more than 500 teachers die in South Africa every year, and it is not possible to train enough new ones to staff schools, many of which have closed. Children often fall sick and there is a high rate of absenteeism, compounded by the frequent deaths of parents. This is further exacerbated by loss of food, homes, and family structure and stability. Hungry, orphaned children cannot be educated, which will result in more poverty and societal breakdown. So many farm workers have died that more than 20% of farms in South Africa are abandoned or minimally productive. Entire industries have shut down for lack of healthy trained and educated workers.

Dr. Coovadia tried to offer suggestions on what should be done, but the problem is so daunting that his proposals do not offer great hope. He pointed out the few successes in Africa, including the impressive reduction in new infections in Uganda, which resulted from government-sponsored education about HIV and the risk of sexual transmission. As a result, the annual incidence of HIV infection among those aged 13-19 years has fallen from more than 4.5% to well under 1% in less than a decade.

Although education and treatment of sexual transmitted diseases, particularly among sex workers and high-risk men, may help to reduce new infections, for the many people in Africa who are already infected the best hope is the possibility of antiretroviral treatment. Although the United Nations has requested $9 billion for this purpose, effective treatment will be hampered by the devastation of infrastructure in the region.

In the second presentation, Dr. John Moore[6] from Cornell University Medical College in New York reviewed the mechanisms of HIV-1 entry into host cells and the current status of drugs under development to block HIV entry, a topic recently reviewed in detail on this Web site. This is perhaps the area of greatest progress in AIDS research during the last 3 to 4 years, and thus represented a dramatic change in tone from the previous talk, as Dr. Moore acknowledged.

Insights into the entry process, including identification of the chemokine receptors and recognition of the interactions that lead to HIV fusion, have identified numerous targets for new therapies. The most advanced of these is the fusion inhibitor T-20, which may be approved sometime in 2002. Monoclonal antibody-based inhibitors of both CD4 and CCR5 binding are effective in vitro and are moving into clinical trials.

Despite the promise of these agents, there are problems. Most are peptides which must be administered by either intravenous or subcutaneous injection. Furthermore, clinical trials with the first 2 inhibitors of CXCR4, the coreceptor used by syncytium-inducing HIV strains, which are associated with accelerated CD4+ T-cell killing and clinical progression, did not demonstrate clinical efficacy; moreover, researchers have seen cardiac conduction abnormalities with inhibitors of both CXCR4 and CCR5. Despite these potential problems, inhibitors of HIV entry are the best hope for new antiretrovirals that act through targets other than HIV reverse transcriptase and protease.

The final presentation, by Dr. Henry Masur[7] of the National Institutes of Health in Bethesda, Maryland, reviewed progress in the management of AIDS-related

opportunistic infections (OIs). The use of multidrug antiretroviral therapy in the mid-1990s led to dramatic declines in OIs, but these diseases have not disappeared entirely and still occur frequently in patients whose CD4+ cell counts have fallen to low levels. Even in patients with a very low CD4+ cell count nadir, an increase in CD4+ cell count in response to highly active antiretroviral therapy (HAART) is associated with reduced incidence of OIs (Figure), and the rate of OIs is low if the CD4+ cell count rises above 200 cells/mm^3, regardless of the pre-HAART nadir level.[8] (Figure)

Prophylaxis has been very effective for many of the OIs, especially *Pneumocystis carinii* pneumonia (PCP) and *Mycobacterium avium* infection. Although PCP resistance to sulfonamides has been recognized, there is little evidence that standard therapeutic or prophylactic regimens are losing their effectiveness, although this remains a concern.

The clinical management of HIV disease has evolved from an initial phase that addressed only the treatment and prophylaxis of OIs, through the availability of antiretroviral monotherapy and dual-therapy regimens, to the current era of HAART that has reduced but not eliminated OIs. The next step may be to incorporate the use of immunotherapy, particularly with interleukin-2 (IL-2), to increase CD4+ cell counts and further prevent OIs. Although it seems that increasing CD4+ cell counts would be helpful, Dr. Masur noted that there are several critical questions that clinicians must ask themselves regarding the use of IL-2 in HIV infection:

1. Are the CD4+ cells that are produced functional, ie, will they help to protect patients from HIV-related complications?
2. Are the short- and long-term toxicities acceptable?
3. Must IL-2 always be given with HAART?

The answers to these questions may be obtained from 2 large multicenter international trials: ESPRIT (in patients with CD4+ cell counts 300 cells/mm^3), and SILCAAT (in patients with lower CD4+ cell counts). These studies together will enroll 6000 patients and will complete accrual next year. In the meantime, excellent guidelines have been published to inform practitioners about the management and prevention of AIDS-related OIs.[9,10]

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41st Interscience Conference on Antimicrobial Agents and Chemotherapy
Day 2 - December 17, 2001

Switching to Trizivir Appears Promising, But With Caveats

W. David Hardy, MD

Chicago, Monday, December 17, 2001 -- Katlama and colleagues[1] reported the 48-week results from the randomized, open-label TRIZAL study (GlaxoSmithKline study AZL30002) that investigated the efficacy, tolerance, and patient adherence to and acceptance of switching from an effective HAART regimen to coformulated zidovudine, lamivudine, and abacavir (ZDV/3TC/ABC [*Trizivir*]).

Study participants, of whom 63% were receiving 2 nucleoside reverse transcriptase inhibitors (NRTIs) and a protease inhibitor, had to have had plasma HIV-1 RNA < 400 copies/mL for at least the previous 6 months prior to study entry, and < 50 copies/mL at study screening. The primary study endpoint was treatment failure defined as virologic failure (2 consecutive HIV-1 RNA levels 400 copies/mL) or premature discontinuation of randomized study treatment by 48 weeks. A total of 209 participants were randomized: 103 to continued HAART and 106 to switch to ZDV/3TC/ABC. The median baseline CD4+ cell counts were 504 cells/mm^3 in the continued HAART group and 482 cells/mm^3 in the ZDV/3TC/ABC group.

The previous antiretroviral history among ZDV/3TC/ABC participants was noteworthy: only 15% had received monotherapy (7%) or dual therapy (8%) compared with 21% of the continued HAART group (14% monotherapy and 7% dual therapy). At 48 weeks, 82 (79%) of the 103 continued HAART participants and 88 (85%) of the 106 ZDV/3TC/ABC participants completed the study.

When analyzed according to the primary study endpoint, treatment efficacy was equivalent in both arms at 48 weeks, with 22% of patients experiencing treatment failure in each arm. At 24 weeks, however, more patients experienced virologic failure in the ZDV/3TC/ABC group; in an intent-to-treat analysis, virologic failure occurred in 5 patients in the ZDV/3TC/ABC group and 1 patient in the continued HAART arm. Three of the 5 patients with viral rebound on ZDV/3TC/ABC had regained undetectable viral load by 48 weeks: 2 remained on ZDV/3TC/ABC and 1 added efavirenz to ZDV/3TC/ABC. Of note, limited genotypic data was presented from the 5 ZDV/3TC/ABC-failing patients. One had reverse transcriptase (RT) mutations to lamivudine (184) and zidovudine (67, 210, 215).

Premature study drug discontinuations occurred in 18 ZDV/3TC/ABC, including 11 (10%) patients with possible hypersensitivity reactions to abacavir, compared with 22 continued HAART recipients. Reductions in median fasting total cholesterol occurred in the ZDV/3TC/ABC group compared with the continued HAART group (-0.80 vs -0.44 mmol/L; $P < .001$) as well as in triglycerides (-0.17 vs +0.01 mmol/L; $P < .001$). Adherence and quality-of-life studies indicated a statistically significant patient preference for ZDV/3TC/ABC ($P < .001$).

Despite considerable technical difficulties with slide projection that caused Dr. Katlama to start and stop her presentation 3 times, this was a scientifically convincing

presentation. The major concern for clinicians should be the lack of data concerning resistance studies in the 5 patients failing ZDV/3TC/ABC at 24 weeks. Because this patient population was preselected for very good to excellent adherence characteristics by virtue of their prior long history of undetectable HIV-1 RNA, it is doubtful that nonadherence was to blame for the virologic failure with the simplified ZDV/3TC/ABC regimen. Previous presentations of similar studies involving patients with viral rebound after switching from a suppressive, protease inhibitor-based HAART regimen to ZDV/3TC/ABC demonstrated archived RT mutations (notably to lamivudine and zidovudine) dating back to their prior therapy with single or dual NRTIs.[2] One wonders if this was also seen in this study; perhaps the technical difficulties and lack of time prevented Dr. Katlama from showing all of her back-up slides. It is hoped that this question will be quickly answered in subsequent presentations.

Reference

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41st Interscience Conference on Antimicrobial Agents and Chemotherapy
Day 3 - December 18, 2001

Update: Structured Treatment Interruptions in Acute and Chronic HIV Infection

Joseph J. Eron Jr, MD

Chicago, Tuesday, December 18, 2001 -- Two posters addressed the use of structured treatment interruptions (STIs) to try to improve HIV-1 specific immune functions, one in patients with primary HIV infection, and another in those with chronic infection.

Miro and colleagues[1] enrolled patients who started treatment within 90 days of onset of symptoms of primary HIV infection, and after at least 1 year of therapy began cyclical treatment interruptions in 12 subjects. Their study provided another lesson in why it is often unwise to describe your results in the title of your research presentation. The title of the poster implies that "almost half" (ie, 5 or 6) of these patients were able to maintain viral suppression off therapy. In reality, only 3 subjects kept their viral load below 5000 copies/mL during the treatment interruptions, and in only 2 of these was the plasma HIV-1 RNA level in the range of 1000 copies/mL or less.

Another problem is that several of the participants were probably not very near to the time of acute infection when they started treatment; several subjects had viral loads of more than 10,000 copies/mL when therapy was initiated. Thus, we do not as yet have strong confirmation of the pioneering work of Bruce Walker's group that suggested that STIs in primary infection might result in immunologic control of viremia.[2]

The results in patients with chronic HIV infection were just as disappointing. Hoffmann and coworkers[3] demonstrated that (1) STIs in individuals who had detectable plasma HIV-1 RNA levels had no real effect on HIV-specific immunity and (2) STIs in chronically infected individuals resulted in an initial *decrease* in HIV-specific T-cell responses as measured by lymphocyte proliferation to p24 antigen stimulation in vitro, followed by an increase back to (or maybe above) baseline in some individuals (although the confidence intervals in the stimulation indices at the time of interruption and after 8 weeks off-therapy seemed to be broadly overlapping).

As Marcus Altfeld and Bruce Walker suggested in a recent editorial,[4] if our goal is to augment HIV-specific immune response (as opposed to reduce toxicity) it might now be time to consider interrupting STI studies in chronically infected patients.

References

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