HOPE AND CAUTION: REPORT FROM THE XI INTERNATIONAL CONFERENCE ON AIDS

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Abstract • Résumé

The XI International Conference on AIDS brought hope to people infected with HIV and to their physicians. The amount of HIV RNA in an infected person's plasma — the viral load — can be quantified to predict the course of the disease and provide a basis for therapeutic decisions. Various combinations of antiretroviral agents can reduce viral load and decrease the risk of progression to AIDS and death. The high cost of these drugs together with the potential for low patient compliance and for the emergence of drug-resistant mutations of HIV represent obstacles to successful treatment. Speakers at the conference explained the dynamics of viral replication and the immune response to HIV infection, and provided preliminary results of studies designed to test the feasibility of eradicating HIV from the body. New guidelines for antiretroviral therapy were presented at a satellite symposium, but the prospects for the long-term success of antiretroviral therapy are unknown.

La XI[e] Conférence internationale sur le SIDA a donné espoir aux personnes infectées par le VIH et à leurs médecins. Il est possible de quantifier la teneur en ARN du VIH du plasma d'une personne infectée — la charge virale — pour prédire l'évolution de la maladie et fournir les bases de décisions thérapeutiques. Diverses combinaisons d'agents antirétrovirus peuvent réduire la charge virale et diminuer le risque d'évolution vers le SIDA et la mort. Le coût élevé de ces médicaments, ainsi que les possibilités de faible observation par le patient et d'apparition de mutations du VIH qui résistent aux médicaments, représentent des obstacles à la réussite du traitement. Des conférenciers ont expliqué la dynamique de la réplication du virus et la réaction immunitaire à l'infection par le VIH et fourni des résultats préliminaires d'études conçues pour vérifier la possibilité d'éliminer le VIH du corps humain. De nouvelles directives sur la thérapie aux antirétrovirus ont été présentées dans le cadre d'un symposium satellite, mais les perspectives de réussite à long terme de la thérapie aux agents antirétrovirus sont inconnues.

International AIDS conferences are marked by a theme, a distinct tone that secures the place of each in the scientific and social history of AIDS. The first conference, held in Atlanta in April 1985, was characterized by shock at the destructive power of the recently discovered virus that causes AIDS. The numbing epidemiologic data heralded the havoc to come. "No test is best" was the slogan of the few AIDS activists who sat politely at tables safely tucked away from the main conference activities. No test was best because physicians had no therapy to offer people who tested positive for HIV.

Optimism and hope primed delegates who attended the XI International Conference on AIDS in Vancouver, July 7–12, 1996. Information provided at the conference represented the result of over a decade's worth of study on the pathogenesis of HIV infection and on the efficacy of dozens of drugs against HIV. AIDS activists, protesting the high cost of medications, had abandoned the 1985 chant in favour of "greed equals death."

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VIRAL LOAD

Viral load, viral dynamics and new antiretroviral (ARV) therapies dominated the scientific sessions of the Vancouver conference. Viral load is expressed as the number of HIV RNA copies per millilitre of plasma and reflects the rate of HIV replication. After the initial burst of viremia, the viral load settles at a baseline value referred to as the "set point." The set point is predictive of disease progression.

Plasma HIV RNA quantification does not measure the total amount of HIV replicating in the body (mainly in lymphoid tissue) but is the best available indicator of the body's total pool of HIV. A laboratory finding that plasma HIV RNA is "undetectable" means that the assay used has a finite limit below which the presence of HIV RNA cannot be detected. That limit varies in different

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studies, from 500 copies or less per millilitre of plasma (as in the Multicenter AIDS Cohort Study) down to 20 copies or less per millilitre (as in the experimental assay used by Incas Study Group). A finding that HIV is "undetectable" in plasma does not mean that it is absent from the plasma or the rest of the body.

If antiretroviral drugs could completely suppress HIV replication, all HIV-infected cells would, theoretically, die a natural death, to be replaced by new, uninfected, cells — achieving total eradication of HIV from the body.

Data from the Multicenter AIDS Cohort Study in the United States convinced delegates that viral-load testing is now the standard of practice for monitoring and treating people with HIV infection. Dr. John Mellors of the University of Pittsburgh described the outcome for more than 1600 study participants whose baseline HIV RNA plasma levels were measured in stored samples. These patients were followed for a median duration of nearly 10 years. Mellors reported on their AIDS-free survival time, their actual survival time and their relative risk of AIDS or death according to stratified baseline HIV RNA levels.

The results were striking. The median time to AIDS or death was 2.8 and 4.4 years respectively among patients with more than 30 000 HIV RNA copies per millilitre of plasma (the highest stratification). Among patients with 500 copies or less per millilitre (the lowest stratification) the median time to AIDS or to death was greater than 10 years. When compared with patients in the lowest stratification, patients in the highest stratification were found to have a relative risk of progression to AIDS or death of 13.0 and 18.5, respectively.

Mellors and his colleagues subsequently developed a complex "AIDS Regression Tree" by which patients can be placed into "branches" according to viral load and then classified within each branch according to their CD4+ cell count. The tree has greater predictive value than viral-load measurement alone.

Mellors suggested that the regression tree could be used "case by case" to accurately predict the course of the disease and to assist patients in deciding when to start therapy. The ultimate goal of treatment, according to Mellors, is to move patients from a high HIV RNA stratification to a low stratification and keep them at that level indefinitely. Mellors believes that this goal can be achieved.

Antiretroviral therapy

An array of clinical trials of ARVs, designed to test the potential of accomplishing Mellors' treatment goal, were flashed before delegates in a stream of presentations. Numerous combinations of standard and unapproved ARV treatments showed varying degrees of HIV RNA suppression, CD4+ cell-count increases and risk reductions for progression to AIDS or death. Many of the trials had been conducted for 1 year or less.

Tantalizing results were reported on the first full day of the conference by one of the conference co-chairs, Dr. Julio Montaner of the University of British Columbia in Vancouver. Montaner reported on behalf of the Incas (Italy, Netherlands, Canada, Australia and the United States) Study Group, which conducted a 52-week randomized, double-blind trial comparing the triple combination of zidovudine (ZDV) plus didanosine (ddI) plus nevirapine (NVP, an experimental, non-nucleoside reverse transcriptase inhibitor) with the double combination of ZDV plus ddI and the double combination of ZDV plus NVP. The trial involved 151 patients who had never received ARV therapy, had never had an AIDS-defining condition, had CD4+ cell counts ranging from 0.200×10^9/L to 0.600×10^9/L and had mean HIV RNA copy levels of 4.2 log10/mL to 4.5 log10/mL. In the triple-combination arm, HIV RNA copy levels decreased by 1.5 log10/mL; at 52 weeks 80% of patients in this group had, by standard assay, undetectable plasma HIV RNA levels. Fifty percent of a small subset of patients who were tested with a newer, more sensitive assay had 20 HIV RNA copies or less per millilitre of plasma after completing 1 year of triple combination therapy.

Is eradication possible?

Montaner's report was quoted widely by other presenters for the duration of the conference. The temptation to muse about the total eradication of HIV from the body was bolstered by a "late-breaker" session held on the last full day of the conference. Dr. David Ho of the Aaron Diamond AIDS Research Center, Rockefeller University, New York City, began the session with a response to an assigned question from the conference organizers: How long should ARVs be administered if they could completely block HIV replication?

Ho began his answer with a review of viral replication and dynamics. He uses a complicated mathematical formula in patients treated with ARVs to calculate the natural "half-life decay" or clearance of HIV by the immune system. This decay takes place in two phases. First or "rapid-phase" decay involves the elimination of free HIV virions in the extracellular fluid plus the loss of productively HIV-infected CD4+ cells. (Ho estimates that 10 billion free virions are produced each day, one half being turned over in 6 hours.) The first phase has a half-life of about 1.25 days. Second-phase decay has a half-life of

13 days and involves the loss of latently infected CD4+ cells and of long-lived HIV-infected cell populations such as tissue macrophages. Ho noted that his mathematical modelling does not take into account "sanctuary sites" such as the brain, where HIV survives for unknown lengths of time, or the possibility of an unanticipated third-phase decay.

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Ho reported on 12 patients who were treated for 16 weeks with ZDV plus lamivudine (3TC) plus nelfinavir (an experimental protease inhibitor). After 8 weeks the plasma HIV RNA level fell from a mean baseline of 150 000 copies per millilitre to 25 copies or less per millilitre, and the CD4+ cell counts increased by over 0.100×10^9/L from a baseline mean of 0.245×10^9/L. These changes in HIV RNA level and CD4+ cell count represented a "profound" suppression of HIV and were sustained for the 16-week trial period.

Ho speculated that if a completely effective ARV therapy existed, a treatment period of 1.5 to 3 years might be sufficient to eradicate HIV. He then put forth two treatment principles to "up the ante" against HIV. First, increase the "pressure" of ARV therapy; second, activate latently infected CD4+ cells and macrophages, leading to the death of these cells. Ho concluded his remarks by stating that "while it is wrong to say we are near a cure, we must try."

Ho's colleague at the Aaron Diamond AIDS Research Centre, Dr. Martin Markowitz, is trying to find a cure. Markowitz reported preliminary results for 8 patients who had completed 4 to 10 months of combined therapy with ZDV plus 3TC plus ritonavir (a protease inhibitor) and whose treatment began within 90 days after infection. Plasma HIV RNA levels fell from a mean baseline of 90 000 copies per millilitre to undetectable levels (500 copies or less per millilitre) in all subjects, and CD4+ cell counts increased from a mean baseline of 0.633×10^9/L to over 0.850×10^9/L.

Markowitz presented detailed information on a representative subject who completed 5 months of therapy. This patient's plasma HIV RNA level fell to 25 copies or less per millilitre, his CD4+ cell count rose from 0.400×10^9/L to over 0.700×10^9/L and the CD4:CD8 ratio returned to normal. No HIV could be cultured from 10 million peripheral blood mononuclear cells. The patient's gp120 antibody and p24 antibody levels (an indication of the immune system's antigen-stimulated antibody response to HIV) decreased significantly. Markowitz concluded that combination ARV therapy had a "profound effect" on the natural history of HIV infection.

Markowitz plans to test the "feasibility of HIV eradication from an infected person." He will first perform a biopsy of lymph-node tissue from patients receiving the triple combination. Because most HIV in an infected person is located in the lymph nodes, eradication would require infected lymph-node cells to be free of HIV. Markowitz may then discontinue therapy in his patients in an attempt to prove that HIV can be totally eradicated from the body.

Markowitz compares treating HIV infection to battling a forest fire. Even if the fire of plasma HIV were completely suppressed, "embers" of HIV in the "sanctuary sites" described by Ho could fuel a blow-up of HIV after drug therapy is stopped. Still, Markowitz is confident enough to test the notion that adequate ARV therapy in recently seroconverted patients can put the fire out completely.

Notes of caution

The idea of eradicating HIV and the success (albeit in trials of short duration) of various ARV combinations caused many hearts to beat faster at the Vancouver conference. But notes of caution were sprinkled throughout the sessions. Delegates were warned of obstacles such as the cost of treatment, compliance problems and the potential for drug resistance that stand in the way of success.

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Dr. Margaret Fischl from the University of Miami School of Medicine estimated the annual cost of providing early combination ARV therapy and monitoring its effectiveness for 2500 patients attending a south Florida clinic at nearly US$22 million. She declared that such costs are not affordable.

Dr. Chaiyos Kunanusont from the Ministry of Public Health in Thailand presented a sophisticated cost–benefit analysis of ARV therapy for HIV-infected adults in his country. His research was conducted in cooperation with the World Bank and the World Health Organization. The results were staggering.

If the Thai government subsidized ARV therapy, the estimated cost of the subsidy divided by the 1996 Thailand national AIDS budget of US$60 million (the "affordability ratio") would be 2.35 for ZDV monotherapy and 6.20 for combination ARV therapy. Kunanusont showed that for the vast majority of Thais infected with

HIV, private payment for ARV therapy would be impoverishing, leaving no money for food or housing.

Kunanusont delivered his findings in a matter-of-fact and undramatic fashion. His was the final presentation at a round-table session on the cost-effective use of ARVs. Regrettably, delegates streamed out as he rose to present his study. Too bad. Kunanusont's analysis was more hard hitting and genuine than the songs of love proclaiming the conference theme, "one world, one hope," at the opening ceremonies.

Worldwide, 90% of people infected with HIV are citizens of developing countries who cannot afford basic health care or adequate nutrition. ARV therapy is unimaginable to those who cannot feed their children.

Dr. Paul Volberding of the University of California, San Francisco, brought the attention of delegates to the problems of the United States in a presentation entitled "AIDS care in the New World." An invited speaker in the conference's Distinguished Lecturer Series, he warned of the perils of managed care, in which private health care organizations give incentives for physicians to spend less time with patients and to generate lower costs. Both goals are incompatible with the proper treatment of HIV infection.

The matter of cost aside, the likelihood of patients taking 17 ARV pills a day indefinitely (as with the ZDV plus 3TC plus saquinavir combination commonly used in Canada) was questioned by some presenters. Asymptomatic patients treated early in their disease can anticipate 12 years or more of ARV therapy, depending on its success, and may well be taking other HIV-related medications. Yet compliance is crucial.

Dr. Jonathan Schapiro from Stanford University in California reported that reduced compliance in patients taking long-term saquinavir monotherapy was associated with increased viral load and the emergence of saquinavir-resistant HIV mutations. The risk posed by low compliance or so-called "drug holidays" was reiterated by various speakers. Missing even one dose of a drug could permit resistant mutations to emerge.

Resistance to combination ARV treatment is feared by both clinicians and patients. Fischl raised the issue of the "durability" of ARV therapy and expressed the view that "immunological recovery" is the ultimate determining factor of the success of ARV therapy.

Understanding the immune response

Scientists, meanwhile, continue to unravel the mysteries of the immune system and its coping mechanisms in the face of HIV. Dr. Robert Gallo from the University of Maryland, as well as other researchers, confirmed the HIV-specific inhibitory role of three recently discovered chemokines: RANTES, M1P-1α and MIP-1β. Chemokines are chemoattractant cytokines associated with inflammation and equivalent to immunologic hormones. They are produced by CD4+ cells, CD8+ cells and macrophages.

Dr. Jay Levy from the University of California, San Francisco, reviewed progress in his search for the soluble CD8+ cell antiviral factor (CAF) that is associated with long-term nonprogression. CAF, not yet biochemically identified, blocks HIV transcription and, in Levy's view, is not the same substance as the chemokines described by Gallo. Levy noted that understanding of the immune response to HIV is at a "Grade 2" level.

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The development of agents that could restore the immune system is at an early stage. Two studies on the intermittent subcutaneous administration of the cytokine interleukin-2 (IL-2) showed dramatic increases in CD4+ cell counts that were sustained for 6 months to nearly 1 year.

Guidelines for ARV therapy: a reasonable concern

Physicians at the conference who wondered how to apply the overwhelming research findings found an answer in a satellite symposium held on July 10. The International AIDS Society — USA (IAS—USA, no connection with the actual International AIDS Society — an unfortunate historical name overlap, according to Volberding, who is a member of IAS—USA) and the Canadian HIV Trials Network, Pacific Region, sponsored the symposium, entitled "Guidelines for Antiretroviral Therapy: Bringing the State-of-Art to Clinical Practice."

The symposium faculty, consisting of renowned AIDS researchers, made up an "international" panel of 13 physician-authors who published an article on the same subject in the July 10 issue of the *Journal of the American Medical Association* (*JAMA*).[1] Reprints of the *JAMA* article were distributed to the several thousand delegates who attended the symposium. Ten of the authors are affiliated with US institutions. Funding for the symposium was provided through "unrestricted educational grants" from 10 corporations, including the major pharmaceutical companies that produce ARVs.

The recommendations made in the *JAMA* article and at the symposium now represent the standard for ARV therapy in Volberding's "new world" of AIDS care.

Plasma HIV RNA quantification (viral load) has been integrated into recommendations for when to initiate or change therapy. But these recommendations are troubling.

Symposium hand-outs directed delegates to the financial disclosures printed at the end of the *JAMA* article. Twelve authors had received financial support from pharmaceutical companies that market ARVs. Two authors owned stock in a company that sells ARVs.

The authors state that, at this time, the development of guidelines for the treatment of HIV infection must "include information from trials in progress . . . as well as extrapolations from studies of the pathophysiology of HIV infection."[1] They list 109 references, of which 29 are abstracts from scientific meetings, one is an executive summary from a pharmaceutical company and two others are reports "in press." The authors' review of ZDV monotherapy makes reference to all major studies except the two (including the Concorde trial)[2,3] that cast doubt on the benefit of such treatment. The Concorde trial dominated the 1993 IX International Conference on AIDS.

Financial involvement should not matter if the recommendations stand on their own scientific merit and have been developed on the basis of all evidence published in peer-reviewed journals. The recommendations published in *JAMA* do not meet this standard and accordingly give rise to a reasonable concern about conflict of interest.

Afterword

The week I returned home from Vancouver I experienced the tonal opposite of the exuberance of the AIDS conference. A voice-mail message on my home telephone informed me that a patient with AIDS had died unexpectedly during my absence. Two patients were admitted to hospital with AIDS complications by the end of my first week back. Whether the XI International Conference on AIDS turns out to be a successful launch to a cure or another step in the Sisyphean struggle against AIDS remains unknown.

References

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Also in this issue is an editorial by Dr. David J. Walters on political aspects of the XI International Conference on AIDS.