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Looking forward to the back of HIV

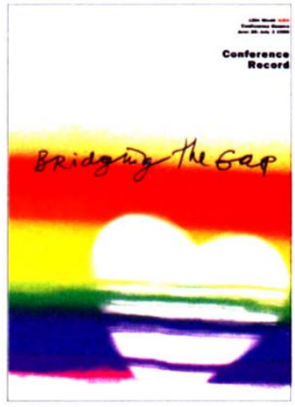
The nature of big conferences—the press desire for specific stories and sound bites, and the gossip and rumor mills that can spread anecdote and impression through the conference community like wildfire—lends itself to the emergence of particular themes and conclusions. Despite calls for cautious interpretation of clinical trial results (*Nature* **382**, 101; 1996), much reporting from the 1996 11th World AIDS Conference gave rise to a near-hysterical sentiment that the then-new antiretroviral drugs were coming close to stopping HIV in its tracks. Subsequent results highlighting the many caveats surrounding the use of these still impressive drugs must have seemed to readers like a bucket of cold water thrown on an overheated press.

Perhaps those attending the 12th World AIDS Conference in Geneva have long memories. Perhaps they are just a little older and more jaded in the face of a virus that has shown itself up to the task of hitting country after country, community after community. Whatever the reason, the mood of last month's meeting was sober and realistic: Whereas drug developments and education programs offer some room for optimism, the sheer size of the global AIDS problem and the ease with which HIV has penetrated unprepared and resource-limited developing countries gives great cause for concern, and the development of appropriate vaccines is likely to be the only long-term solution.

The Haves and Have Nots

Perhaps most despair was felt by those visiting Geneva from poor countries that are seeing huge increases in the size of their HIV-positive populations yet have little hope of any useful antiviral drug therapy to treat the infected. Almost all those presenting work at the conference made mention of the growing discord between those able to offer drugs to their patients and those able only to offer a shoulder to cry on.

The recent UNAIDS/ WHO *Report On The Global HIV/AIDS Epidemic*, summarizing numbers as of the end of 1997, estimates that 89% of the world's 30 million HIV-positive people are to be found in sub-Saharan Africa and the developing countries of Asia—the very countries that can least afford to deal with the problem. Among them they account for less than 10% of the global gross national product. This means that despite the technically impressive performance of protease inhibitors and other sophisticated anti-HIV drugs, they are unlikely to have any effect on nine of ten infected people.



This disconnect runs far deeper than drug availability. By and large, the same countries that have no access to the drugs are also seeing the steepest rise in infection rates; the largest number of orphans who have lost both parents to the disease; the weakest medical infrastructure for dealing with complications associated with the infection; and the most work to be done in educating their communities about the risks and how to avoid them.

It is disturbing to consider that in the absence of a dramatic turn of events (a therapeutic vaccine effective in these communities, or a scheme for global access to at least one or two anti-HIV drugs), almost all of today's 30 million infected people will mostly go untreated and die of this disease in the next five to ten years. Even more disturbing is the UNAIDS/WHO estimate that in 1997 alone, nearly 6 million new infections took hold. Given that most of the infected people do not yet know they are carrying the virus, it is likely that 1998 will see even more new infections, meaning that annual deaths from AIDS are going to increase before they decrease. Therefore, the most urgent need in these very vulnerable countries is for fast and effective education programs that can help reduce the size of the next wave of potential AIDS patients.

There is one area in which many of the most vulnerable countries are well ahead of the US—needle exchange (*Nature Med.* **4**; 648, 1998). With good reason, many speakers, activists and delegates deplored the recent Clinton administration decision not to fund community needle exchanges for intravenous drug users. This atrocious situation is indefensible and this administration and others like it should be taken to task as the number of needless deaths after infection from contaminated needles rises.

Limitations of antiviral drugs

Even in those rare countries with good access to the best antiviral therapy, disturbing trends in treatment have emerged. First, the best proven treatment for HIV infection is probably a combination of three or four drugs and the different requirements, characteristics and side effects of the drugs means that they must be taken in tightly defined, demanding regimens—so demanding that this can often be the undoing of the treatment. Second, viral resistance has always been a looming threat. Now it is estimated that 30–50% of patients on triple therapy have at least some resistance to one or more of the few available drugs. Third, the combination of a demanding drug regimen that can limit long-term adherence, drug–drug interference and simple clearance dynamics means that often the drugs are not present consistently in a patient at the required levels. These the three problems

contribute to what John Mellors (University of Pittsburgh) estimated might be a 50% failure rate for HAART (highly active anti-retroviral treatment).

Emerging drug resistance deserves special mention. Simon Wain-Hobson (Pasteur Institute) pointed out that although the chance of a virus developing resistance to any given drug can be viewed simply as a stochastic event, it is important to note that like many viruses, HIV displays a tremendous mutation rate that hastens the chance of resistance developing. External events can also influence the speed with which resistance emerges. If viral counts are kept at a minimum, so too is *de novo* drug resistance. However, if viral levels start to rise, perhaps for the reasons mentioned above, the opportunity for resistance to emerge is increased. As discussed by Mike Saag (University of Alabama), both at the individual patient level and the patient population level, resistant virus has a replicative advantage and is therefore likely to rapidly find its way into the community. And increasing single-drug resistance inevitably leads to multiple-drug resistance—a very dark cloud on the horizon.

All these issues represent a major challenge to the pharmaceutical industry. Can drugs be improved to reduce side effects, simplify schedules and eliminate drug–drug interactions? Can new drugs be developed quickly to replace those overwhelmed by resistant virus? And is there a will and a way to make these drugs available to more of those that need them?

The International AIDS Conference is much more than just a conference—if it were not for the very sobering thought of what AIDS is doing to the world, it might better be described as a festival. The 12th conference, held in Geneva last month, certainly lived up to this reputation: 14,000 registered participants, including representatives from more than 70 countries; 940 members of the press; and 800 volunteers. There were 5,000 posters (chosen from 7,100 submissions) and 400 oral presentations organized into 9 concurrent sessions. Displays from 100 commercial exhibitors and 160 non-governmental nonprofit organizations graced the halls. Keeping everyone in touch were a daily conference newspaper and 250 computers (networked with the help of 10 km of cabling) with email and internet access and daily live webcasts to the outside world. All this was crammed into six full days of challenging, informative and superbly organized interchange that forced for the most part productive discussion, some argument and much understanding. If you are going to run a huge international conference, this is the way to do it. The organizer, Bernard Hirschel, and his collaborators are to be congratulated!

Latent infection

Although it has been known for some time that latent infection must exist in patients who have seen their viral loads drop below the sensitivity of current viral assays (when these patients stop HAART, the virus rebounds quickly and vigorously), the many variables make estimates of the total latent pool and its dynamics difficult. Likewise, it is unknown where the virus hides.

Using even the most sensitive viral assays (that can detect as few as 20 viral particles/ml), it seems that HAART can clear free virus from the circulation quickly and easily. However, populations of long-lived infected cells present more of a challenge. New data from David Ho (Aaron Diamond AIDS Research Center) and colleagues suggests that in the order of 10^4–10^6 HIV-infected resting, memory CD4 cells may be present in a patient even when assays can detect no circulating virus. Assuming a half-life of a little less than six months for these cells, it may take 5–10 years to eliminate this pool of infection. Adding to this bleak outlook is evidence that there may be a residual low level of virus replication in this pool.

The bottom line is that it is unlikely that HAART alone will be able to completely eliminate HIV from the patient. Ho speculates that it may be possible to stimulate the resting infected cells such that viral replication kills the cell and the resulting new virus is quickly neutralized using HAART. Alternatively, if a sufficiently low level of latent infection can be achieved, an endogenous anti-HIV immune response may be able to either finish the job or at least maintain the virus at low levels for the life of the patient. This in itself may be difficult as it is known that both HIV-specific antibody and CTL numbers are inversely correlated to virus load. Something other than soaring virus levels will be needed to stimulate either humoral or cellular anti-HIV activity.

Vaccines

Given the failure of antiretroviral drugs to reach 90% of the world's HIV-positive patients, and their inability to completely eliminate the virus even in those treated aggressively with HAART, the research community must turn over even more resources to the development of therapeutic and protective vaccines. From the Geneva conference, it seems that this is beginning to happen: Advocacy groups such as AVAC (AIDS Vaccine Advocacy Coalition) and IAVI (International AIDS Vaccine Initiative) are getting into their stride, the commercial sector is committing major new resources to the challenge, global organizations are providing more funding (*Nature Med.* **4**, 750; 1998), UNAIDS is putting into place ethical guidelines governing vaccine trials (see page 874), and the US Office of AIDS Research has highlighted vaccine development as an area to receive more attention (see Nathanson, page 879).

This level of interest and activity is necessary in the face of the many hurdles to be overcome. On top of the questions that face those designing any vaccine, there are many issues that are particular to the development of an anti-HIV vaccine. Michel Klein (Pasteur Mérieux Connaught) outlined how at a very fundamental level it is unknown just what sort of an immune response is required for protection to be complete—to what extent do humoral responses need to be complemented by a cellular response, and will mucosal immunity be required? It is also unknown if individual vaccines will be effective across the different HIV clades. And perhaps the biggest unanswered question concerns the choice of viral components to act as immunogens. Many researchers consider the absence of a suitable animal model in which to address these and other points and in which to test prospective vaccines a major impediment to progress.

The first anti-HIV vaccine to reach phase III trials will soon be administered to groups in the US and Thailand (*Nature Med.* **3**, 753; 1998). Although many researchers are pessimistic about the chance of this vaccine demonstrating protection, this trial should nonetheless be seen as a positive move. The research, pharmaceutical, medical and HIV advocacy groups are no longer talking about when and if vaccines should be tested, but instead are discussing which vaccines should go to trial. This represents a significant cultural change in the community and is likely to quicken the pace of vaccine development both by those willing to test many candidate vaccines in the hope that they will 'strike gold' and those who prefer first to precisely define the necessary components a successful vaccine must have. But there can be no doubt that vaccines are the only intervention likely to have a long-term affect on the virus.