

Where Do We Stand with the AIDS Epidemic?

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Introductory Comments

I feel very honored to have been asked to give this year's Hilleman lecture, not only because it affords me the opportunity to visit the Children's Hospital of Philadelphia but also because Maurie Hilleman and I go "way back." I believe it was in the mid70s, when I was a young and opinionated advisor to FDA and he was an imposing legend in the vaccine world, that I sassed him for the first time. I did the same thing to Albert Sabin and he didn't take it well; but Maurie did, and what's more, he made it clear that I had captured his interest, and over the years we became friends and increasingly close colleagues. Shortly after I became Dean at the University of Michigan School of Public Health, he visited as a distinguished lecturer, and that's when we had our first, intense conversation about the new epidemic of AIDS.

I have an ambitious agenda for today's talk, so I am going to try to resist the urge to tell Hilleman stories; but one stands out in my memory. It was in late 1993, at an unofficial, closed meeting to discuss "future directions in AIDS research." My late dear friend, Howard Temin, had been instrumental in initiating it, and in attendance were most of the key figures in AIDS from biomedicine, government, industry, public policy, and (in abundance) ACT-UP. By the nature of the epidemic, most of the people were much younger than me – and without question Maurice had almost a half-century "head start" on the ACT-UP folks and was clearly the senior person in the room. I had the privilege of chairing the discussion, and it was an intense and vigorous two days, with many of the passions and sorrows flowing in a sometimes vituperous torrent of frustration. ACT-UP people really knew how to make their opinions known!

I think I may have been one of the few people there who knew Maurice and was aware of his extraordinary record of contribution to human well-being. And those who **do** know Maurice will not be surprised to hear that he is capable of turning the air blue with his language when he so decides – which he did there. I still remember my great amusement when, at

the reception that evening, the young kids who had imagined themselves so radical came up to me one by one and said "Who is that guy?" (sort of like Butch Cassidy and the Sundance Kid). He won their total respect, not the least because of his facility with four-letter words, and thus was able to contribute and be listened to at a pivotal moment in the AIDS debate.

I would like to keep on going in that vein, but time forbids. As I said, I am most honored to give a lecture in a series that honors such a giant and such a friend!

I do have some ambitious goals for this talk. First, I want to give a quick historical review of the AIDS epidemic. To people entering the health professions now there must be a feeling that AIDS has always been with us; and yet it was less than twenty years ago that all this began, and I believe we should be duly awed by what a dreadful tragedy unfolded in our lifetimes. On the upbeat side, it is also remarkable to realize how far we have come, and that helps to give perspective to the challenges now facing us. Once I have done that, I will comment on some of the current issues of biology, prevention, health care and public policy that pertain to the on-going HIV/AIDS pandemic. And along the way I will share with you my "worry list" – for, to put it mildly, I am deeply concerned about where we stand with the AIDS epidemic, and even more troubled by our complacency about it.

A Brief History of the HIV/AIDS Epidemic, with the Advantage of Hindsight

So, down to business. Let me start with that brief history of the AIDS epidemic, with the advantage of hindsight. Once upon a time, perhaps a few decades ago or maybe one hundred years ago or so, a primate retrovirus found a way to cross from its host species to humans. As you probably know, the so-called species barrier is quite key in virology, and the current analysis of the origin of human viral pathogens is that they made the species jump to humans through close proximity and/or unusual opportunity. The classic book that set forward that hypothesis was William McNeill's Plagues and Peoples, published in 1976, which I commend to you, for it is thoughtful, persuasive, and of ever greater importance as we face the generic problem of emerging infections. Indeed, the substrate for the current hot debate about xenotransplantation relates directly to the concern that one might inadvertently facilitate such cross-species adaptation of unknown pathogens.

Obviously no one can pinpoint the precise time or way in which what we now call human immunodeficiency virus type 1 began to infect people; nor can one be sure of its initial host species, although very recent data make chimpanzees a good bet. There is little doubt that HIV-2 made the jump from smaller primates to humans, and did so quite recently.

All of that is fascinating, but off the point. The truly important fact is that, somewhere around the early 1970s, HIV-1 "got legs", to use a current phrase, and became a newly **pandemic** virus. It had established very viable means of transmission, had probably existed for many years in isolated rural enclaves, and then – with the help of urbanization, social disruption and international travel – circled the globe quite efficiently, seeding every continent and most countries within a decade of the time it began its travels. Thanks to its capacity to establish asymptomatic infection for an average of ten years prior to expression of illness, it got a remarkable, disastrous head start, so that when it first surfaced clinically in 1980 and 1981, it was far ahead of those who tried to stop it.

When I talk about the AIDS epidemic, I am regularly amazed as I remind myself that it was **indeed** less than twenty years ago that we first became aware that a strange new infectious disease phenomenon was unfolding. It is hard to recreate the sense of confidence that had prevailed up until that time, at least so far as infectious diseases were concerned. In fact, *hubris* is a better word, strongly reinforced just a decade before by the U. S. Surgeon General's assertion that infectious diseases were a thing of the past and that it was time to turn away from them to other, more important topics.

Happily, not everyone accepted that admonition, and it is important to say, before we go any further, that Maurice Hilleman played a truly unique role in preventing what could have been a complete collapse in the vaccine world, stemming from neglect and disinterest. I entered the public policy arena in 1973 as a member of the Viral and Rickettsial Vaccine Efficacy Review panel for FDA, freshly charged by Congress with undertaking a systematic review of the generic **and** specific product licenses of all existing viral and rickettsial vaccines. The process took six years and during that interval, for virtually every vaccine extant, there was an attrition of manufacturers from several down to one – and in most instances that **one**

was Merck, prodded to continue on in that shrinking and relatively unprofitable territory by its scientific director, Dr. Hilleman.

Furthermore, in fruitful and important collaboration with others, that same decade of the '70s saw Hilleman and colleagues not only create hepatitis B vaccine but test it carefully and with sufficient rigor that the stored sera and data were available for re-visitation as our awareness of HIV and AIDS dawned in the early '80s. There were many giants in that time, but none stood taller than Maurice.

Anyway, as you know, in the summer of 1981 the first reports appeared in CDC's Morbidity and Mortality Weekly Reports of a novel syndrome of profound immune suppression in young, previously healthy men whose sole unifying characteristic was participation in a lifestyle that included unprotected sexual activities with many, many same-sex partners. Quickly thereafter it became clear – if one was watching without bias – that drug users, heterosexual partners of drug users (whether male or female), hemophiliacs, and some of the newly born offspring of ill women were joining the ranks of the dead and dying. Unhappily, many people in important public policy arenas had already circumscribed the potential reach of this devastating new illness in their thinking. Homophobia set the tone, with what came to be called “addictophobia” following close behind. To quote a famous infectious disease scientist in the mid-eighties, it was perceived as affecting “just gay men and drug users,” to which comment he added that we shouldn't over-react because (again quoting) “...it will burn itself out.” !! What an awful price we paid for that dismissiveness – it was the first of many proofs during subsequent years that one could not make headway against this pathogen while dismissing whole categories of people and violating human rights!

The further story unfolded inexorably, as you are well aware, and time forbids my telling much of it. It became apparent quickly that the rest of the world was caught in the same scary path of that new/pandemic virus; that for the first time human disease was clearly linked to a retrovirus; and that, once the blood supply was protected, while daunting biomedical challenges lay ahead, the very limited modes of transmission open to HIV made it possible to interrupt further spread by low tech **behavioral** interventions. ✓

All of that was evident by the mid80s, at a time when AIDS cases could still be counted in the few thousands. I remember another giant of the ✓

time, Jim Curran (then of CDC – now Dean of the School of Public Health at Emory) saying two wise and profoundly disturbing things as the epidemic began to escalate. First he said (in 1982, I think) that it was easy to hold public attention while a very few cases were at issue, but it would get much harder as the numbers rose dramatically. I was still mostly a biomedical scientist at that time and I thought I had heard him wrong. Surely people would care more and more, in proportion to the increasing carnage? Sadly, I heard him right, and it was a sage comment that we need to remember and learn from. I suppose it reflected not only the hostile thinking I alluded to before, but also the intrinsic human foible that gives rise to the saying: “Familiarity breeds contempt.”

The other thing he said, in about 1986 after the very limited modes of transmission of HIV had been firmly delineated, was (again quoting): “Someday people will be shaking their fists at us, saying ‘Why didn’t you tell us?’ ...and that’s going to hurt, because we did!” As I got to know more and more parents coping with the impending, premature loss of their children of all ages, that haunting comment came back to me time and again. We learned so much about prevention in those early years, and yet those lessons go unused or underfunded, and certainly undervalued, to this day.

I can’t leave the topic of Jim Curran without making one tangential comment. He really was a hero in the early years of AIDS, returning repeatedly and forcefully to a message his bosses didn’t want to hear. I say that because anyone who saw the HBO version of Randy Shilt’s book, And the Band Played On, will surely have come away with the impression that Jim was, at the very least, part of the problem rather than the key mover toward solutions. That’s false, misrepresents the book, and (I am told) made Randy Shilts most upset with HBO during his dying weeks – he protested but failed to win the day. Take it from me: Jim Curran was a true hero!

Current Status of the Epidemic

So where are we now? Well, as Jim Curran implied, **numbers numb**. So let me try to give them poignancy and meaning despite their massive scale. In the United States, in eighteen years, we have lost more young Americans to AIDS than died in all the armed conflicts since the Civil War! Currently the CDC cumulative death toll stands at ^{nearly 400,000}; another 300,000 or so have AIDS, and an estimated ^{600,000} are infected but not yet aware of it. Perhaps the worst number of all is the conservative estimate that at least

40,000 new infections occur annually – a figure that has not changed for a number of years. It is sometimes pointed out proudly that that new-infection number is down from 150,000 per year in the late 1980s; but to give you perspective, the steady state of 40,000 rivals the peak number of paralytic polio cases in the worst epidemic summer before the creation of polio vaccine. It is cause for embarrassment and shame, not complacency! And of course, those new infections are stoking the clinical fires for the foreseeable future. One key concept that we must grasp is that, unlike the early years of this saga, **there is an enormous amount of HIV out there, waiting to be spread further as we let our guard down.**

One of the complexities inherent in discussing all this is that many, if not most, statistics pertain to people with AIDS, rather than HIV. That is understandable, since it is easier to be sure of the numbers; but it is crucial to realize that, in so doing, one is plotting a course using a snapshot of the terrain that is a decade out of date. This is a dynamic, unstable epidemic that is by no means under control, and so it is useful and important to look at trends in the U. S.

And there are ominous trends to report. Each year more women are diagnosed with AIDS; that has been true from the beginning, so that last year they constituted over 30% of newly diagnosed individuals. With the homophobic mind-set I described earlier, the infection of women was routinely ascribed to drug use; yet a recent CDC study found that of new infections in women, 75% are due to heterosexual exposure and only 25% to drug use. That should be no surprise, since worldwide data have long indicated that three-quarters of HIV/AIDS results from heterosexual spread – and as I used to like to say, contrary to occasional suggestion, we Americans are **not** a different species. It does, in any event, have profound implications for prevention programs.

The central role played by injection drug use must not, however, be minimized, and in the United States the concurrent drug use epidemic constitutes a real “wild card.” Whereas most sexual transmission is mercifully inefficient, especially when “safer sex” measures are taken, sharing of injection apparatus is extraordinarily effective and lends what I think of as “flash-fire potential” to orderly epidemiologic predictions. In cities around the world it has been documented that populations of injection drug users have gone from less than 1% infected to as much as 90% infected in just one year’s time. It is an erratic dynamic but obviously a potentially

explosive feature of the American scene, since to this day it is still the case in this country that treatment for drug addiction is virtually inaccessible to **poor** addicted persons. When we declared war on drugs, we made no provision for the prisoners of that war, and our primary therapy for drug addiction at present is incarceration! ✓

Another trend that is of deep concern is the disproportionate involvement of communities of color with each passing year. That would be troubling in any event, but it is complicated dreadfully by feelings of mistrust arising not only from the perceived racism that ~~constitutes a stain on~~ our society so deeply, but also specifically by the continued reverberations stemming from revelations of the so-called Tuskegee study. I hope you all know about that: beginning in 1932, for forty years a government-sponsored observational study was carried out on African American men in rural Alabama, purportedly to study the natural history of syphilis. Even the basis of the study was racist in its implications, but most shocking of all was that it was only discontinued in 1972, with the men having never received treatment for syphilis when it became available. That word "Tuskegee" haunts every conversation one can have in communities of color, and efforts at prevention are seriously impeded by its shadow. (Parenthetically, it is perhaps a cruel irony that the Tuskegee revelations and the human immunodeficiency virus probably made their debut in this country at almost exactly the same time!) My dear, late friend Jonathan Mann, the creator of the World Health Organization's Global Program on AIDS, pointed out eloquently and repeatedly that violations of human rights were, in and of themselves, a risk factor for HIV/AIDS. **Our** national experience attests to that: last year more than half of all newly diagnosed cases of AIDS were in African Americans.

There is one final trend I want to mention, especially to this audience: even at the beginning of the epidemic it was estimated that fully 20% of people with AIDS had acquired their infection during their teenage years. CDC now says that over half of new HIV infections are occurring in people under the age of 25, and **half** of those cases are in women. In a sad analogy to the smoking saga which David Kessler termed "an epidemic of youth," HIV has found a durable target in our adolescent kids. Adolescence is an age of experimentation, and now some of those experiments have turned deadly. We really have a duty to warn!

On the Upbeat Side...

Up to this point I have been talking gloom and doom, I realize. That isn't the whole picture, of course. There are wonderful success stories across the whole spectrum of endeavor that reflect the intense efforts of thousands of researchers, dedicated government officials, health care professionals and community-based care-givers. The most dramatic is (or at least was) the achievement in the early 1980s of a drop in seroincidence from 18% per year to 0% per year in the San Francisco gay community, with comparable results in New York City as well. These astonishing changes resulted from intense, community-based efforts at education for prevention. I don't know of another demonstration of behavioral intervention that had such stunning results. But sadly, the lessons are getting lost or forgotten, or blurred beyond effectiveness by a generation gap made worse by the terrible death toll of past years. Young gay men are openly dismissive of preventive messages, or else they embrace the excessive optimism of the new therapies and decide it's worth the risk. In any event, we must not forget that it was possible and **did** happen once upon a time.

The second wonderful advance stems from the so-called "076 study" in which treatment of pregnant women with AZT during the latter part of pregnancy and during the peripartum period, followed by oral AZT for six weeks to their newborns, decreased the HIV transmission rate from 25% to 8% -- a dramatic two-thirds decline. Those initial results and subsequent efforts to refine and extend them have resulted in a steep drop in the number of new cases of pediatric AIDS in this country and in parts of the world where such intervention can be afforded. While I have some concerns about this set of policies and procedures that I will discuss later, we should surely celebrate that achievement.

A third factor -- one that tends to fade from memory -- is the remarkable success achieved in virtually freeing the blood supply of HIV and, in the wake of that accomplishment, of a number of other potential pathogens as well. In the beginning years of HIV's silent spread, contamination of the blood supply resulted in a massive viral assault on the hemophiliac community; it is estimated that fully half of the 20,000 people with severe hemophilia in the U. S. who were dependent on factor VIII concentrate for their well-being were infected. And by 1983 blood transfusion itself was recognized as risky. You can barely imagine how exciting and important it was when it became possible, in 1985, to test

donated blood for HIV antibodies and remove infected units. With time those blood screening tests have become more and more sensitive and specific as technology has made it possible to identify viral RNA early in infection. The number of new HIV infections occurring through this route plummeted and now is in the single digits. That is surely a cause for celebration!

And then there are the highly active antiretroviral therapies. Prior to 1987 there were no antiviral drugs for HIV; then came AZT. It certainly improved the situation compared to nothing, but its clinical effect was variable and time-limited (primarily because of viral drug resistance), and something more was clearly needed. Therapy for opportunistic infections, prevention of *Pneumocystis carinii* pneumonia, and other interventions also helped. But in 1995 data emerged suggesting that combining several new anti-retroviral drugs of at least two classes (in terms of mechanism of action) could actually drop so-called HIV "viral load" below the limits of detection.

By mid-1996 the standard of care had changed beyond recognition as had the clinical outcome for some people with HIV. The highly active antiretroviral therapies, as that general approach came to be called, had a Lazarus-like effect for many young people whose prospects for survival were fading. Suddenly community-based agencies that had been immersed in matters of hospice care and hospital insurance were faced with additional new tasks such as job-retraining and placement. Again, I have some worries to express about all this, but for the moment, let us rejoice in such therapeutic success. It surely represents a bright beam of hope across a landscape that had been totally dark and foreboding!

Oh yes – one other success story. Given the absence of treatment for addiction that I mentioned before, some remarkably brave and defiant community activists began their own (usually illegal) programs of needle exchange in an effort to assure that addicted people would at least have the means to remain free of HIV. Those programs almost invariably resulted in a number of things: first of all, participants quickly sought treatment for their addiction when that option was available, and their very participation gave a venue for education about safer sex and the like. Second, it could be shown that drug use did **not** increase in communities where needle exchanges were available. And finally, it was painstakingly shown that transmission both of hepatitis B and of HIV were indeed significantly decreased by that intervention. That having been said, it is still the case that federal funds

cannot be used to support such needle exchange programs. And, in the more salient context of treatment for addiction, the mayor of New York has even seen fit to interject his own reading on pharmacology, asserting that methadone treatment for heroin addiction should last no longer than six months – in full defiance of the data.

A Few Comments About the Global Pandemic

Switching gears for the moment, let me make a few comments about the global HIV/AIDS pandemic. As it turns out, we truly are a “global village,” and lessons learned in one place are often edifying in many others. Reverting to my role as historian, for the moment: I am sure you are aware that AIDS expressed itself first in the developed countries, in the Caribbean and in subSaharan Africa. You may not be aware that it started rather spottily in Latin America, and was relatively late coming to Eastern Europe and to Asia – at least so far as reporting went. The time intervals here are not great, and the delay in disease expression meant that time to warn was short and perhaps illusory, but we did try. In 1987 Jonathan Mann and Jim Chin from the World Health Organization, and I (posing as a WHO person as well, since Asia didn’t want American advice) set up and staffed a conference in Sydney. It was hosted by the Australian government and was designed to try to get “ahead of the curve” in Asian countries that had thus far been spared. The ministers of health from 27 countries around the Pacific Rim were in attendance and for five days we interspersed diplomatic niceties with intense sessions which were designed to say “Watch out, it is surely coming to your land soon!”

The result was sadly instructive. Toward the end of the week one after another of the ministers of health stood up and said something like: “We have had two cases of AIDS in our country, but they were foreigners....” Or “We had a case of AIDS, but it was in someone foolish enough to have traveled to America.” In short, we uncovered massive denial. And I guess that is the point of my story – throughout the world, denial was the uniform first response to AIDS. And believe me, it mattered!

For instance, Uganda went through years of official denial that anything was wrong while thousands and thousands died of what was called “slim disease” – a major form of AIDS in which tissue wasting is the predominant manifestation. Their seroprevalence had reached double digits and their resources were meager. Then the Ugandan government – for a

complex variety of reasons – did an about-face and made AIDS a priority. Today the turn-around in incidence of new infections there is truly dramatic, even though the resource base hasn't improved noticeably.

The same kind of trend reversal occurred in Thailand, where the universal conscription of men in their late teens, coupled with some sexual mores that intensified the possibility of transmission, led to a truly alarming epidemic in which one out of five conscripts was found to be infected by the early 1990s. After much internal difficulty, a wonderful man named Mechai finally won his battle to have the government take notice; and in subsequent years the prevalence of HIV in conscripts has dropped from double digits to about 5% -- an especially notable feat in view of the prevalence of drug use and sexual tourism within the country.

Anyway, denial seems to be a universal first response – and that is another take-home lesson, for HIV already starts with a ten-year lead time, and we simply give it a further advantage with each failure of national will. In 1993 I visited South Africa for the Kaiser Family Foundation, and during that visit met with the nation's AIDS leaders. They knew then that AIDS was coming, that seroprevalence in some areas was already at 6%, and that if they did everything they knew how to, they might be able to hold it to 6% nationally by the year 2000. They also told us that, if they did **not** pull out every stop, it would be at 25% by then; and as that milestone approaches, the latter projection turns out to have been "right on." In fact southern Africa, spared in the very first years of the epidemic on that continent, now promises to be the scene of greatest AIDS devastation, threatening the inspiring and robust moves toward justice and democratization that should properly occupy their full attention.

In Eastern Europe – another area that had a brief window of opportunity – a different dynamic joined with denial to set the stage for what is now a fulminant situation. Tragically, the sense of release that came with glasnost and all that followed opened the way for widespread drug trafficking – something that had not occurred to any major extent under the former totalitarian rule. Even in health care settings, re-use of injection apparatus had been a common practice, so the concept of not sharing needles fell on particularly foreign soil. The result has been a rapid invasion by HIV of the newly independent eastern European states. It is a recent enough event that the full impact is yet to be felt by health care systems staggered by the other elements of disruption in those societies.

And finally, back to Asia. That 1987 conference I alluded to did not succeed in its main goal. Denial persisted well beyond reason and continues to this day in places like China. India maintained its posture of non-involvement for an astonishingly long time; even in 1990 the Indian government was declaring that only a few prostitutes in Bombay were infected, and inferred strongly that India was likely to escape the pandemic. By now the official Indian governmental estimate is ~~of~~ 3-4,000,000 cases of HIV infection, and the likelihood is that the number may be much higher and, for a variety of societal reasons, has truly explosive potential. ✓

In brief, then, less than 20 years after the first recognition of AIDS and thus of HIV, there is not a single country that does not have the virus within its borders. The conservative estimate of HIV seroprevalence globally is 40,000,000; and the expectation is that the countries of Asia – which, of all peoples, had the greatest possibility of learning from the experiences of others – will constitute fully 40% of the epidemic by next year. And stay tuned – there might be much more to come, as I will get to at the end – for HIV-1 is evolving rapidly, and the global response is not keeping pace. ✓

Some Specific Issues of Current Interest

1) HAART

Before I get to that, though, let me turn to some specific topics that are timely and bear comment. The first of these is the matter of the highly active antiretroviral therapies – that is, the combined antiviral drug approach which I mentioned earlier that was instituted widely in the United States and the developed world in late 1995 and 1996. [For ease of discourse I will simply refer to these as “antivirals” and will not try to be specific about particular drugs or their combinations and permutations].

As I am sure you know, their initial clinical impact, as measured in extensive, carefully monitored clinical trials, was striking – in fact it might be fair to say “dizzying.” At the Vancouver International AIDS meeting in the summer of 1996 the elation of scientists and clinicians and some in the HIV community was so loudly proclaimed that it effectively drowned out voices of concern and caution. To a large extent that is still true, at least insofar as public discussion is concerned. One hears or reads statements

like: "It's almost over!" or "...only a couple more drugs and we'll really be there."

Even in Vancouver that made me shudder, and I had only a minimal grasp then of how problematic things were going to get. Don't get me wrong: many, many people who thought they were goners have been given a whole new life. That's wonderful! AIDS has, since 1992, been the leading cause of years of productive life lost in the United States and we need all our people with their talent and energy intact. And the hope infused into some communities is uplifting. It is vastly better than the frustrated hopelessness of the early years that led so commonly to "burnout" and despair.

Yet these therapies are fraught with difficulties and complications. First, the regimens are amazingly demanding, as such things go. One must take some pills on an empty stomach, some only with meals, and all of this several times a day. If the person in treatment already has one or several of the opportunistic infections of AIDS, we can be talking about literally dozens of pills a day – try doing that if you are homeless or have no regular access to potable water! And then there is the toxicity: for some people the toxic side effects are sufficiently severe that they have made the agonizing decision to go "off therapy" rather than submit to the dismal effect the regimen has on their life style and sense of well being. Between issues of cost, access and ability to tolerate the toxicity, no more than 50% of patients in care are able to sustain the course of treatment. As you probably know, it was once hoped that the drugs could be discontinued after one or two years, but those wishes have been dashed by recent findings – so we seem to be talking about a lifetime's worth of therapy.

A couple of additional issues concern me about the highly active antiretroviral therapies. It goes without saying that they are costly, and it is not surprising to learn that they intensify problems of access to care. But the efforts to divert resources to pay for antiviral therapies have subtle and unintended side effects of their own, for a hostile Congress has not increased overall funding and money is therefore diverted from programs of prevention in order to pay for AIDS drugs. Furthermore, whereas in the early years private donations were readily solicited, that is getting much harder now as once-generous donors succumb to the false but comforting notion that "it's over, or at least nearly over."

Turning to a much more troubling feature of the new therapies: antiviral drug resistance is **already** a reality. In fact, the reason the combination approach to treating HIV infection was taken in the first place was because the virus had shown a marked ability to develop resistance to any one antiviral over a relatively brief time. Even at the outset it became clear that resistance could and would develop with the new regimen as well, but it was felt that **perfect compliance** on the part of patients would reduce that risk to an acceptable level. It was even said, right out in public, that only "responsible" people should even be considered eligible for the highly active antiviral drugs.

The facts about resistance are considerably more complex, and do not submit readily even to the most compulsive of pill-takers. Highly motivated people with HIV or AIDS have maintained the regimen diligently, only to go from viral loads that are undetectable to pre-treatment levels of HIV RNA right in the midst of their compliance. Within the AIDS community, this is well known to occur and is referred to as "crashing," I'm told. And, be assured, it is well demonstrated that resistant virus can be (and is) transmitted by the usual routes. The price we will pay for therapeutic overconfidence and inattention to prevention is almost surely going to escalate soon.

2) AIDS and Pregnancy

Let me turn, now, to the subject of treatment of pregnant women and/or their infants for HIV, another topic that I touched on briefly before and told you was on my worry list. The 076 protocol that gave the first exciting results was complex, intensive and extensive. It also begged the question of who was getting treated since it presupposed that anyone eligible would be receiving prenatal care at least by the final third of gestation – not always the case, as you know.

Subsequent efforts have been made to adapt that protocol in a couple of ways: first, it looks as if one can treat mothers beginning only in the peripartum period with considerable effect, and that treatment solely of the infant is a viable option, although not as effective. Furthermore, efforts are well underway to test the effectiveness of the highly active antiviral therapies in this context, which in a way is a relief since we were in a truly awkward stance there for a while, insisting on the one hand that no adult should be treated with a single antiviral, but on the other insisting that

pregnant women receive only AZT. That problem will take care of itself soon, I guess. Notice, however, that while the follow-up studies of infants (infected or not) who have received the 076 regimen have thus far been reassuring, there is far less experience with the combination-therapy drugs. As pediatricians I feel we should remain alert to late-appearing effects, since these drugs interact with DNA and we are giving them to fetuses and newborns, whether HIV-infected or not.

Another point of note in this regard is more troubling still: all these programs to prevent and/or abort neonatal infection leave the mothers untreated! And it is my strong impression that the single most important predictor of child health is maternal health and well-being. In fact, there was an interesting study done in the early AIDS years in subSaharan Africa, right after the serologic test for HIV became available. It looked at infected vs. uninfected mothers and their infected or uninfected offspring, and measured infant mortality from **whatever** cause at the end of one year. Sadly but not surprisingly, diarrheal disease exacted a substantial toll. Infants born to HIV-positive mothers had a significantly higher mortality rate – but the real central finding of that study was that the worsened prognosis pertained **whether the infant was HIV-infected or not**. It matters greatly whether a child has a mother, and so the failure to build 076 and subsequent protocols around mother-and-child treatment is of great concern to me.

That point is brought home still further by the breast feeding issue. As you may know, it was thought early on that breast feeding only occasionally resulted in transmission of HIV from an infected mother to her nursling. However, that was wrong. If one lets an untreated, HIV-infected mother breast feed her infant for two years, the likelihood of infection doubles. It is a hard case in parts of the world where other threats to infant survival are more dire and immediate. But failure to address the **many** circumstances surrounding HIV infection and pregnancy – adequate prenatal care, access to safe water and infant nutrition, and the on-going health of the mother – all loom over the wonderful but fragile success of the neonatal HIV treatments.

3) HIV and Substance Abuse/Addiction

Turning to another topic: I have already said much of what needs saying about the interface between substance abuse and HIV/AIDS. They are two epidemics that are so tightly interlaced that anything done to hurt or

help in one of them may have a parallel effect on the other. There is much that we could do that we are not doing! Drug treatment "on demand" would make a substantial difference. Increased availability of known treatments such as methadone, increased utilization of new treatments coming "on line," (thanks to the good work of NIDA), and stop-gap implementation of needle-exchange programs and other interventions shown to be effective – all of those things would help a lot. It is difficult to overstate the importance of injection drug use in the future of HIV – and we are not using what we know!

4) AIDS Vaccine: What Would We Do With a Good One?

Now I get to a tough issue, and one that I must deal with carefully – that is the matter of AIDS vaccines. Please listen closely as I say that I strongly support the emphasis and effort going into development of one or several AIDS vaccines. In many parts of the world success in such an effort may spell the difference between demographic disaster and ultimate recovery from the ravages of AIDS. But I have focussed my remarks today primarily on the United States, and here I contend that there will be very little use for such an intervention.

You must know that the very best vaccines we have are 95- to 98% effective, not 100%. Furthermore, that effectiveness pertains to epidemic conditions – measles, for instance, comes and goes, leaving a huge population of resistant kids and recurring with a fresh batch of susceptibles. We have seen, with measles, that when even the small fraction of non-responders is exposed in settings such as high schools or colleges to the importation of fresh measles strains, a brisk epidemic can erupt. Similar dynamics pertain to most of the vaccine-relevant infectious diseases.

In my mind it is no accident that there is no vaccine at present that is effective against a sexually transmitted disease. [Hepatitis B is a technical exception, but it is also quite different from the other sexually transmitted diseases in having a major antibody-mediated host response that proves to be effective against the virus]. People have tried, to be sure, with gonococcus and chlamydia and others – but whether it is the increased "pressure" of repetitive exposure or the relative flimsiness of mucosal immunity or something else – for whatever reason, those efforts have so far proved ineffectual.

Now take HIV: there has yet to be demonstrated a naturally occurring form of protective immunity that could be imitated. It is, indeed, sexually transmitted, which means that vaccine protection would need to last throughout the sexually active decades of recipients, and which also raises the issue of secretory and mucosal immune response. It has, as its preferred target, the very cells of the immune system that one supposes would be important in dealing with such an agent. It has a striking capacity to change its antigenic "spots," and within the same host the isolates can be shown to have changed sufficiently over time to render invalid the earlier immune responses that do occur.

Thus the sheer scientific difficulty of vaccine creation is formidable. But as I said a moment ago, it is terribly important that the effort be pursued with diligence and creativity. My guess is that the AIDS vaccine, when it comes, will be very different from the more familiar vaccines we rely on at present. Happily, there are new and innovative approaches underway and increasing support for the effort.

Just for the moment, let us assume that those feats are accomplished. What would we, in the United States, do with such a vaccine? Perhaps we would deploy it in the health care setting – although that is a far less risky venue than has been implied. Perhaps there would be some communities or situations in which its benefit/risk analysis would be favorable – although always one would have to keep in mind that the goal is to **prevent HIV infection, not simply to mount a vaccine program**, so behavioral interventions would need to be maintained.

But the group at increasing risk, as I noted before, are adolescents, and here I think we had better pause. We are already having trouble getting support for the very rational idea of having a second round of immunizations as kids approach the teenage years – they are practically **out** of the health care system by that time and it is really tough. Should immunization be done when sex and drugs become a risk? And when is that? In view of the startling data accruing about pre-teen sexual and drug-using activity, adolescence clearly is too late. Fifth grade? Third grade?...but now we are begging questions that got C. Everett Koop in trouble even when he was simply advocating rudimentary preventive education.

How many parents would object to having their children immunized against HIV? And out of those how many would refuse out of conviction?

Out of ignorance? Out of outrage at the imputation that they and theirs were even part of this epidemic risk? If you wonder what I mean by that, think how many parents would rush to have their children protected by a gonococcal vaccine! The denial of STDs goes far to explain today's rampaging epidemics of other sexually transmitted pathogens as well as the tragic astigmatism that has blunted our response to AIDS.

Sad to say, I think there would be parental denial of two kinds, both of which would enrich the future of HIV. There would almost surely be a sizable number who would not participate at all with a vaccine program just as they object to AIDS education; but there would probably be an even larger number who would leap at the chance to **substitute** immunization for the need they are just beginning to acknowledge to talk to their kids about sex and drugs!

I have drawn this out a bit because, along with the false complacency brought by the highly active antiretroviral therapies, we are poised to take a hit from the euphoria that is sure to accompany any progress on the vaccine front. Both are varieties of denial which (as I have said repeatedly) is our worst enemy in this battle.

5) A Final Concern: HIV-1 subtypes and Emerging Infections

Finally, let me turn to an issue I almost hate to bring up – that is, the continuing emergence of HIV-1. As I noted at the outset, there are two distinct species of HIV, HIV-1 and HIV-2. While HIV-2 is not exactly benign, it is in almost every way less of a problem than HIV-1 and has remained relatively geographically limited to West Africa. However, HIV-1, the culprit in the worldwide pandemic, was found early on to exist in several subtypes, referred to by letters. Subtype B is the strain that spread early and rapidly around the developed world; subtypes A, C and D began the early outbreaks in subSaharan Africa (as well as elsewhere).

But then a truly scary thing began to happen. HIV has a diploid genetic structure, and as new subtypes began to appear, it became evident that under some circumstances – specifically, co-infection of a single cell with two subtypes – **recombination** could occur. That is a far more daunting prospect than the tendency to mutations of which we were long aware. There have now been at least half a dozen instances in which specific individuals have been found to harbor two different subtypes **and**

their hybrid simultaneously. The list of subtype letters now goes to at least M, and there is every reason to suspect it will lengthen. Each subtype has its geographic domains; but given the fact that the groundwork for emerging infections has been so well laid, I believe we are really courting disaster to be cavalier about HIV at this critical juncture. I assure you, we have samples of virtually every subtype now circulating in the U. S. It may be that we've barely begun to appreciate the full awe of HIV.

Conclusions

There. I am out of time, and have probably spoiled your day. Sorry about that – but I find it hard to maintain an upbeat tone when talking about AIDS these days because I see the situation as truly ominous. As I tried to detail, the advances of molecular biology, virology and immunology have taken us farther and faster than one could have dreamt twenty years ago. Yet our habitual reliance on biomedicine and high technology has also led us astray and we are in trouble if we don't regroup quickly. I have a favorite good news/bad news joke that goes as follows: an airline pilot comes onto the intercom during a long flight, saying "Well, folks, I have some good news and some bad news. The good news is, we're making great time. The bad news is, we're lost."

That's putting it too strongly, for I don't think we are totally **lost**. But we must revisit the lessons learned during these difficult twenty years – that **only by a combination** of high science and "low tech" social and behavioral interventions can we make progress. And above all, we must learn, before it is too late, that violation of human rights and dignity is, in and of itself, a prime risk factor for HIV and AIDS. I cannot think of a better way to close than with a quotation from a speech made by Jonathan Mann to the World Health Assembly eleven years ago. He said (and I quote): "We live in a world threatened by unlimited destructive force, yet we share a vision of creative potential – personal, national, and international. The dream is not new – but the circumstances and the opportunity are of our time alone. The global AIDS problem speaks eloquently of the need for communication, for sharing of information and experience, and for mutual support. AIDS shows us once again that silence, exclusion, and isolation – of individuals, groups, or nations – create a danger for us all."