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TAG
Treatment Action Group

tagline

NEWS ON THE FIGHT FOR BETTER TREATMENT, A VACCINE, AND A CURE FOR AIDS

Premature Aging and HIV
New Links Provoke Mystery, but Research Lags

People with HIV may experience low-level inflammation that erodes health and shortens life spans—even after their virus is undetectable.

BY BOB HUFF

A recent and growing worry in the AIDS treatment community concerns premature aging and shortened life spans in people with HIV—despite complete suppression of the virus by successful antiretroviral therapy.

Reports of increased risk for heart disease, kidney disease, cancers, dementia, bone weakness, and frailty in people with HIV even when their viral load is undetectable seem paradoxical, but the concern is real. In an era when antiretroviral drugs are better than ever and when fewer people in the United States are at risk for developing the classic diseases of AIDS, why do the bodies of some people with HIV seem to grow old before their time?

The common assumption holds that inflammation is the culprit. Chronic, low-level inflammation has been implicated in atherosclerosis, and impaired blood flow may contribute to heart and kidney disease and problems with cognitive function. People with uncontrolled HIV replication often have increased blood markers of inflammation, and these chemical markers may not completely normalize after antiretroviral drugs have stopped the virus. It's possible that HIV-associated immune activation is directly causing the inflammation, though that is not proven. Other factors may also foster premature aging. Rates of smoking are high in cohorts of people with HIV. Drug toxicity is a possibility. Hepatitis C virus or other, subclinical infections might cloud the picture. Even chronic stress and worry could contribute.

What is responsible for the signs of premature aging in people with HIV who have undetectable virus?

Yet there are strong suggestions that HIV is the underlying issue. But what might be responsible for premature aging in people with HIV who take antiretroviral drugs and have little or no virus in their bloodstreams? For some people, unfortunately, it appears that simply stopping viral replication may not be sufficient to restore normal health.

Is It the Virus, the Body, or the Drugs?

The first possibility to consider is that HIV causes permanent damage to the body and its immune system within days or weeks of infection.

Leading scientists now think that immune cells in the intestinal tract are among the earliest targets of HIV when a new infection is first established. Within a few weeks, HIV ravages the immune defenses of the gut and demolishes a large proportion of the body's CD4 T-cell reserves. With this breakdown, the theory goes, bacteria and other microbes that normally stay in the gut begin to cross the unprotected border and enter the bloodstream in a process termed *microbial*

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WHAT'S INSIDE

translocation. The "leaky gut theory" maintains that these foreign invaders are met by a bodywide immune response that revs up to destroy and expel them. This systemwide activation of immune cells, some say, is like throwing gasoline on a fire, since HIV infects the very cells that are multiplying to defeat the bacterial interlopers.

If an important swath of an individual's immune capacity is irreversibly wiped out during this frantic initial phase of HIV infection and CD4 cell destruction, then the body may never quite recover—even if HIV replication is subsequently controlled.

A second possibility (and none of these excludes the others) is that the body's immune capacity slowly and permanently diminishes over time as HIV replication persistently erodes the CD4 cell population, and the count of CD4 cells per cubic millimeter of blood—a key marker of HIV progression—declines. Medical guidelines for offering anti-HIV treatment use the falling CD4 count as a signal for when to start therapy. While the CD4 cell count recommendation in U.S. guidelines has risen from 200 to 350 in recent years, the normal range of CD4 counts runs from 500 to well over 1,000. In most people, CD4 counts will not drop to the 350 level for many years after infection—years in which HIV is actively replicating and possibly destroying unrecoverable immune capacity. It's possible that when treatment is finally started—and even when the virus is quelled—it is too late to reverse permanent immune damage. If this is the case, then the lowest point of CD4 decline, called the CD4 nadir, might be an important predictor of subsequent premature aging.

A third possibility is that very low levels of HIV can contribute to altered immune regulation—even when the virus has been undetectable in the blood following years of successful treatment. Some viral proteins are known to send signals to the immune system and cause problems even when they are not part of infectious viral particles. Although viral replication may be halted by drugs, HIV is not destroyed in the body. Its DNA is stitched into the genomes of the cells it has infected—and some of these cells (millions, actually) can quietly persist for years, occasionally generating bursts of viral fragments or even whole viruses that show up as "blips" in viral load tests. If these viral proteins can signal the immune system to respond inappropriately when there is no immediate threat, then the inflammation caused by this state of semipermanent activation might contribute to the symptoms of premature aging in people with no apparent HIV in their blood.

A fourth possible explanation for premature aging in people who are successfully controlling their HIV infection with antiretrovirals points to the drugs themselves. Careful comparisons between drugs in clinical trials and sophisticated analyses of large databases have revealed which medicines are most likely to cause problems. The worst offenders have been identified as members of the NRTI class of anti-HIV drugs, and several have been removed from HIV treatment guidelines. NRTI drugs were the first anti-HIV agents discovered, and they have formed the backbone of antiretroviral treatment regimens ever since. Newer-generation NRTI drugs are generally considered by doctors to have very low levels of toxicity that are easily managed in most people who take them. But long-term experience with some drugs notwithstanding, very subtle negative effects on health may be occurring that cannot be clearly identified until studied in a large clinical trial. Drug toxicity has been recognized as causing metabolic disorders and problems with how and where tissues such as fat and bone are created and destroyed in the body. One NRTI drug recently downgraded from "preferred" status in treatment guidelines has been associated with an increased risk for heart disease in certain patients with other serious risk factors for heart problems like family history and smoking. Another widely used drug has been linked to low levels of kidney damage, though the evidence is contradictory. However, other drugs are so ubiquitous in HIV regimens that no rigorous comparison studies have been conducted that might reveal their role in premature aging. These highly effective drugs are far safer than earlier NRTI drugs, and the benefits are currently thought to far outweigh the risks. But if these medicines are having a subtle, chronic impact on the body's aging process, it will be hard to pin down that effect until a new set of clinical trials can be undertaken.

The consensus on when to begin HIV treatment is slowly shifting to higher and higher CD4 cell counts.

Premature aging in people with HIV who have successfully suppressed their virus with antiretroviral drugs is still a vague and unproven problem. But the early warning signs are there.

Where Is the Research?

Research is needed that can better describe the phenomenon of premature aging in people with HIV and elucidate what may be causing it. Some of this research is already underway; some has yet to be planned.

A new treatment strategy that uses no drugs from the NRTI class is being tested in a few small pilot studies. These trials may give the first glimpse of the role that NRTI drugs—even those with no apparent toxicity—are playing in the subtle, long-term effects of HIV infection on aging.

Another treatment strategy being tested calls for adding a highly effective new-generation drug to a conventional regimen to intensify pressure on the virus and push down HIV replication to levels well below what is currently considered "undetectable." Whether this approach can prevent production of residual HIV or toxic HIV fragments that disturb the immune system is uncertain, and new types of drugs and assays may have to be developed to determine whether there is ongoing immune damage despite viral control. The ultimate goal of this research is to permanently eradicate HIV from the body.

The consensus on when to begin HIV treatment is now shifting toward starting treatment earlier during infection, when CD4 counts are higher. As evidence increasingly suggests that any period of

uncontrolled HIV replication is harmful—even if there are no apparent outward signs or symptoms—then medical opinion may eventually abandon the CD4 test and decide that HIV treatment should begin as soon as the virus is diagnosed. A large clinical trial that compares starting therapy using current guidelines with starting therapy much sooner also plans to look at the signs and chemical markers of premature aging. This trial, a follow-up to the trial that first illuminated the premature aging problem, should provide some important answers about the risks of letting HIV go untreated.

If the damage done during the first few days and weeks of HIV infection has lifelong impact, then it will be difficult to treat, short of finding a way to repair the injury. Most people are unaware that they have become infected, and even if they experience symptoms of acute infection, it may be too late to repair the devastated immune cell population. More research is needed to understand these early events, but one "experiment in nature" may help illuminate what is going on. Clinical trials are being conducted to investigate the possibility of preventing HIV-negative people at high risk for infection from acquiring the virus by giving them antiretroviral medications before they are exposed. The idea is that the drugs may stop an infection from taking root—hence the name of the concept, preexposure prophylaxis, or PREP. But since no treatment is perfect, some people using PREP will inevitably become infected despite having the drugs in their bodies. This has already happened at least once, with the provocative apparent result that, even though the infection was not blocked, the intensity of the initial impact of HIV may have been blunted by the drugs and the individual's subsequent viral levels seem to be partially controlled. A follow-up study of this individual and others may lead to an important understanding of what HIV is doing in the body during those crucial early days after infection.

One unsolved barrier to understanding the subtle effects of HIV on aging is that any treatment that reverses premature senescence will take a lifetime to prove. While inflammation is strongly suspected as a factor in shortening the life spans of people with HIV, there is as yet no conclusive link and no easy-to-use laboratory marker that can indicate when a treatment has had a beneficial impact. The tests explored by immunologists to date represent a plethora of unvalidated markers determined by procedures that vary from lab to lab. So far, no "smoking gun" better than the CD4 count has been proven, and CD4 counts are only very general indicators of immune capacity; we need to understand what is happening well before CD4 counts begin to drop.

Premature aging is a growing concern among people with HIV and their doctors. The factors that may be responsible are not well understood. While some studies are being done, the basic scientific research that could explain the underlying mechanisms is fragmented and underfunded. Though the prospect of premature aging may seem of secondary concern in a disease that only a dozen years ago produced nearly inevitable early death, discovering whether there is a link between inflammation and the premature degradation of the mind and body is of interest to all. ●

TAG Sponsors "Cure Meeting" in Washington D.C.

In November 2008, Treatment Action Group, the Foundation for AIDS Research, and the FAIR Foundation sponsored a meeting of leading scientists in Washington, D.C., to discuss the possible avenues—and impediments—to finding a way to eliminate HIV from the body—or at least cause long-term, drug-free remission. Among the sponsors, the Workshop on Eliminating Viral Persistence and Eradicating HIV Infection was informally known as the "Cure Meeting."

Hopes of permanently curing HIV infection deflated after it was discovered that the virus inserts its DNA into the DNA of its target immune cells. New viruses are made as a by-product of the cell's transcribing DNA to perform its normal functions. Some of these infected immune cells can quietly hide in lymph nodes for years, harboring a hidden reservoir of virus. When a wave of powerful new treatments were approved in the mid-1990s, it was hoped that over time the reservoir cells would die off and the infection would eventually burn itself out. Mathematical estimations of this scenario soon showed that—even if perfect suppression could be achieved—it could take 20–60 years to eradicate HIV from the body with drugs alone. After that disappointment, hopes for a cure dimmed as science turned to the more realistic goals of improving treatments and discovering a vaccine.

In 2007, the first of a new class of drugs called integrase inhibitors was approved by the FDA. The new drugs work by preventing the viral DNA from inserting itself into the immune cell's DNA and some think they may pose a nearly impenetrable barrier to new infections. The potency of integrase inhibitors has stimulated interest in bringing virus levels far lower than had been previously thought possible and has revived talk of eradicating HIV. But the long life of the infected reservoir cells is still a problem.

One approach to flushing the reservoir has been to stimulate the resting cells into action, thus luring out the hidden HIV so it becomes susceptible to antiviral drugs. Early attempts used agents that stimulated the immune system indiscriminately, and were scuttled by toxicity. Some scientists are now proposing ideas for stimulating hidden HIV-infected cells with greater precision. Others think it may be possible to identify the cells and specifically target them for destruction. Still others think it may be possible to permanently switch off mechanisms in the cells that HIV depends on for replication.

Many scientists say they have good ideas that need to be tested in people but cannot obtain funding because the current grant mechanisms of the National Institutes for Health (NIH) are not oriented toward supporting translational research that moves therapies from the laboratory to the clinic. Other barriers involve FDA guidelines for how research can be performed on people; some of these requirements limit what university-based scientists can accomplish on limited budgets.

The Cure Meeting invited key leaders from the NIH; other, nongovernmental funders of AIDS research; top scientists working in the field of HIV persistence and eradication; doctors involved with cutting-edge HIV studies; and HIV treatment activists. Discussion was divided between roadblocks and opportunities, both in the science and in the funding and practical spheres.

TAG plans to follow up on the directions outlined at the meeting with an advocacy campaign aimed at revitalizing research to permanently defeat HIV.

Start Me Up
Questions Linger on Initiating and Switching HIV Treatment

When and how to start antiretroviral therapy—and how to respond down the line when changes become necessary—remain unsettled questions.

BY TREATMENT ACTION GROUP

Amid a plethora of therapeutic options, gaps remain in our understanding about when and how to start antiretroviral therapy—and how to respond down the line, when changes become necessary.

By 1996, HIV treatment had been revolutionized by using a wave of effective new antiretroviral drugs in combination, and by the development of viral load testing that showed HIV dropping to undetectable levels after treatment was started. Within months, the falling death rate from AIDS confirmed the impact of the treatment revolution beyond question. A dozen years later, better drugs and refined treatment strategies have made antiretroviral therapy much safer and even more effective. However, despite a flood of information from drug approval trials and treatment strategy studies, key questions have yet to be settled, such as: When is the optimal time to start HIV treatment? Which drugs should be used first? And which drugs should be used after the first have failed?

In April 1998, the first U.S. HIV treatment guidelines were issued. These guidelines were intended to avert therapeutic chaos by identifying preferred drug regimens. Since then, the U.S. Health and Human Services HIV Treatment Guidelines panel's recommendations for when to start HIV treatment by CD4 cell count have veered from <500 cells/mm^3 (1998) to anywhere between 200 and 350 cells/mm^3 (2001). As of 2007, the guidelines recommend initiating treatment when CD4 cell counts fall to 350 cells/mm^3. But the primary goal of therapy—suppression of HIV replication to the lowest possible level—has remained constant.

It has become increasingly clear that in addition to the deadly opportunistic infections and cancers of AIDS, long-term, untreated HIV infection also increases a person's risk for kidney, cardiovascular, and liver disease, as well as for certain non-AIDS cancers. This is alarming news given that so many people in the United States are not diagnosed with HIV until they already have very low CD4 cell counts. In 2005, the Centers for Disease Control (CDC) reported, a staggering 38% of people testing HIV-positive were diagnosed with AIDS within 12 months of their HIV diagnosis.

Many doctors and activists now argue that the serious non-AIDS consequences of untreated HIV—along with advances such as drug combinations that are more convenient, less toxic, and require less-frequent dosing—call for starting treatment much earlier than current guidelines recommend. Yet the fundamental question—when to start—has not been formally studied in a large randomized controlled trial designed to produce strongly convincing data. Instead, experts interpret results from cohort studies, treatment interruption trials, and nonrandomized studies to inform treatment guidelines.

With a lull in new HIV drug approvals expected over the next few years, a perfect opportunity exists to do some serious research on these key treatment strategy questions: When should HIV treatment be started? What drug regimen should one start with? And how should subsequent drug regimens be chosen?

The latest HIV drugs to enter the market (darunavir, maraviroc, raltegravir, and etravirine) were initially studied in treatment-experienced people who had multidrug-resistant virus. Unlike some of their predecessors, these drugs may also be appealing options for treatment-naive people due to favorable side effect profiles, potency, and the (yet to be proven) assumption that they will remain effective and easy to tolerate for a long time.

Obviously, the first HIV regimen a person chooses has important implications for subsequent treatment options. So far, HIV drug development has focused mainly on treatment-naive people or people with multidrug-resistant HIV. Less is known about optimizing what comes between these two poles: second- and third-line regimens. Current guidelines offer comprehensive information on drug characteristics, side effects, and potential drug-to-drug interactions, and recommend resistance testing in case of virologic failure. But the choice of what drugs should be used after the first regimen fails is more by default than by design, leaving many doctors to guess.

More data on incorporating the latest generation of drugs into the most effective, durable, and least toxic regimens—and what to follow them with—are urgently needed. Studies are currently examining some of these new combinations for first-line therapy, but they aren't designed to shed light on questions about subsequent treatment sequencing. Trials are needed that investigate switching to improve tolerability and avoid metabolic side effects, in addition to those that study how to respond to treatment failure.

HIV treatment is a lifelong prospect. It is time to examine treatment strategies that can be relied upon for the long haul, not just at the beginning and the end of therapy. ●

Bacterial Breakout
New Studies of Microbial Translocation

Immune activation has become a central culprit in the latest theories of how HIV causes disease. But despite increasing research on the question, the sources of immune activation continue to puzzle scientists.

BY RICHARD JEFFERYS

The term *immune activation* is frequently encountered in the context of HIV research, but exactly what it means can be unclear. In a general sense, immune activation can be thought of as the mobilization of immune system cells that occurs during a battle with a pathogen. In most cases, immune activation is transient and subsides as the immune system either eliminates the pathogen or brings it under long-term control. What makes HIV (both HIV-1 and HIV-2) infection different is that immune activation does not fully resolve after initial infection but instead persists, eventually increasing as CD4 T-cell counts decline and progression to AIDS occurs.

A couple of years ago, Jason Brenchley and his colleagues at the National Institute of Allergy and Infectious Disease identified what may be a key contributor to immune activation in HIV infection: the leakage of normally "friendly" gut bacteria out of the gastrointestinal tract and into systemic circulation, a phenomenon called *microbial translocation*. Over the past several months, a number of new research reports have confirmed and extended Brenchley's main findings. In parallel, an immunology study in mice has hinted that the causes of microbial translocation in HIV infection may be more complex than originally thought. This new research has potential implications for both pathogenesis and treatment.

Activation Background

Activated immune system cells express certain molecules on their surface, which can be measured to get an idea of the magnitude of immune activation occurring in an individual. In HIV infection, the expression of the molecule CD38 by CD8 T cells has proven the most useful measure of immune activation; elevated levels were cited in the very first AIDS case reports in 1981 (at that time CD38 was known as T10). In the early 1990s, UCLA researcher Janis Giorgi showed that levels of CD38 expression on CD8 T cells correlate with HIV disease progression. Several studies have since reported a closer

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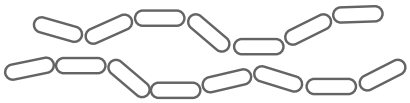
Bad Bacteria

Studies Suggest Microbial Translocation Contributes to Liver Disease and Neurological Impairment in HIV Infection



Liver Disease

Systemic lipopolysaccharides (LPS) resulting from microbial translocation have been associated with alcohol-induced liver disease, via interactions with liver macrophages (called Kupffer cells) that promote production of proinflammatory and profibrogenic cytokines. This led Ashwin Balagopal and colleagues from the Johns Hopkins Medical Institutions to study the role of microbial translocation on liver disease progression among individuals coinfected with HIV and hepatitis C. Their results, published in the July issue of the journal *Gastroenterology*, showed that CD4 T-cell depletion is strongly associated with microbial translocation. In a cohort of 29 individuals with pre- and post-HIV seroconversion samples available, a decline in peripheral blood CD4 counts to less than 200 was associated with significantly higher levels of LPS compared to participants whose CD4 T cell counts remained above that threshold.

In a larger group of 88 individuals with either cirrhosis or minimal liver disease, progression of liver disease was found to occur 19 times more frequently among individuals with levels of LPS in the highest quartile compared to those with levels in the two lowest quartiles. The study authors supplemented this analysis with a look back at stored samples from 53 members of this cohort for whom samples were available from at least eight years prior to the ascertainment of their liver disease status. Compared with baseline, a statistically significant elevation in levels of LPS became evident during the year prior to the development of liver damage, but not before. In discussing these results, the researchers point out that untangling the cause-and-effect relationship between microbial translocation and liver disease will require additional studies, as their data cannot completely rule out the possibility that liver disease caused the observed microbial translocation, as opposed to the other way around. They also stress that causality could plausibly go in both directions.

HIV-Associated Dementia

In the journal *PLoS One* in June of 2008, Petronela Ancuta and colleagues from the Dana-Farber Cancer Institute in Boston published data showing that microbial translocation is associated with the development of HIV-associated dementia (HAD). The impetus for the study came from prior findings that LPS induce the activation of immune system cells called monocytes and thus increases monocyte trafficking into the brain; these events appear key in precipitating HAD. Ancuta evaluated levels of LPS in a cohort of 119 people with AIDS and found that they were associated with HAD independently of HIV viral loads and CD4 counts. The researchers also discovered that intravenous heroin use, alcohol use, and hepatitis C coinfection were all associated with higher levels of LPS in their cohort.

association between CD38 expression and progression than is seen with viral load measurements. In monkeys, immune activation has also emerged as the key factor in determining whether infection with SIV (HIV's simian sibling) causes disease; some monkey species develop persistent immune activation and progress to AIDS, while others show little or no immune activation and do not develop disease despite relatively high viral loads.

Despite this appreciation of the role immune activation plays in pathogenesis, the mechanisms by which it occurs are yet to be fully elucidated. At the time of initial infection, activation appears largely driven by responses to HIV. The immune system then typically gains some degree of control over HIV replication and activation subsides to a set point that correlates with the viral load set point and also predicts the pace of subsequent disease progression. However, in just about all HIV-infected people (including most long-term nonprogressors), immune activation levels remain significantly higher than those seen in uninfected individuals. Although it is likely that immune responses to HIV contribute to persistent activation, HIV antigens alone are insufficient to explain the phenomenon. Other persistent coinfections (such as hepatitis B or C) have been shown to contribute, but immune activation and disease progression still occurs in individuals who are not coinfected.

Translocation Indications

The search for additional causes of immune activation led to Jason Brenchley's study, which was published in *Nature Medicine* in 2006. Brenchley found that people with progressing HIV infection and AIDS (but not acute or early stage HIV infection) have significantly elevated levels of bacterial products called lipopolysaccharides (LPS) in their bloodstream compared to uninfected individuals, and that levels of LPS correlated with CD38 expression on CD8 T cells. As the research paper notes, levels of LPS are a widely accepted indicator of microbial translocation, which has been reported to occur in a number of other settings including burn injuries, gastrointestinal surgeries and after the use of T cell–depleting cancer chemotherapies. Brenchley also confirmed the presence of biologically active LPS in the bloodstream of people with HIV by demonstrating that soluble CD14 levels were increased in parallel; CD14 is a molecule from immune system cells called monocytes that is both secreted and shed from the cell surface after stimulation by LPS. Brenchley and colleagues speculated that the likely cause of microbial translocation was the rapid, early depletion of gut CD4 T cells that occurs during acute HIV infection.

Poor immunological responses to ART have been attributed to elevated levels of immune activation.

Microbial Translocation and Immune Reconstitution on Antiretroviral Therapy

One potential issue with using levels of LPS as a marker of microbial translocation is that it is not a direct measurement of the presence of bacteria. An alternative approach is to use polymerase chain reaction (PCR) to look for bacterial DNA in the bloodstream. Jason Brenchley has presented this type of analysis at conferences, reporting that bacterial DNA (called 16s DNA) correlates with levels of LPS, but these data have yet to be published. Consequently, a research letter by Giulia Marchetti and colleagues in the October 1, 2008, issue of the journal *AIDS* represents the first published direct evidence of microbial translocation in HIV infection.

The aim of Marchetti's study was to assess whether microbial translocation impacts CD4 T-cell recovery after starting ART. The researchers recruited 24 individuals dubbed "immunological nonresponders" (INRs) who were compared to 11 people with good CD4 reconstitution ("full responders" or FRs) and 12 controls with advanced, untreated HIV infection. An initial evaluation of plasma levels of LPS showed that they were significantly higher in both INRs and individuals with untreated, advanced HIV infection compared to FRs.

Echoing Brenchley's data, levels of LPS also correlated with markers of immune activation. The PCR technique was then employed to measure bacterial 16s DNA in samples, and sequencing experiments were conducted in order to confirm that the DNA was derived from gut bacteria species. Using this method, Marchetti and colleagues showed that 16s DNA could be isolated from 5 out of 7 INRs and 6 out of 12 individuals with advanced HIV infection, but none of the 7 FRs evaluated.

The results are consistent with the idea that microbial translocation contributes to immune activation in HIV infection and also indicate that it is associated with poor immune reconstitution despite viral suppression. However, in terms of the mechanism by which microbial translocation may be occurring, Marchetti and colleagues raise an interesting issue when discussing their results. They note microbial translocation may contribute to the lack of an immunological response following viral suppression by antiretroviral therapy (ART), but also point out that—conversely—persistently low T-cell counts might be causing microbial translocation. In their more technical language, "bacterial translocation might be favored in INRs by reduced T-cell-mediated competence failing to provide full immune control in mucosa and mesenteric lymph nodes, thus permitting peripheral egress and survival of bacteria."

This distinction may be important. Poor immunological responses to ART have been attributed to elevated levels of immune activation in several prior studies. But Marchetti and colleagues are suggesting that causality could go in the opposite direction as well: a failure to restore CD4 T cells may allow persistent microbial translocation, which in turn causes persistent immune activation.

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The Hepatitis B Data Void
Making Treatment Decisions in an Evidence-Free Zone

New drug development; treatment strategies; natural history; long-term outcomes: The lack of support for research on hepatitis B virus is putting millions of people with the virus at risk.

BY LEI CHOU

People living with chronic hepatitis B (HBV) and their doctors have been struggling with a lack of clear guidelines for making treatment decisions—despite advances in new treatment options made during the last decade. High cost, indefinite duration, potential long-term side effects, and the emergence of drug resistance—all have raised the stakes on finding optimal HBV treatment strategies. In the cold light of evidence-based science, the lack of research on HBV natural history and on long-term clinical outcomes was brought into sharp relief at the NIH Consensus Development Conference on the Management of Hepatitis B held October 20–22, 2008, in Bethesda, Maryland.

The NIH Consensus Development Program has convened meetings to develop evidence-based consensus statements on medical controversies since 1977. Sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases and the Johns Hopkins School of Medicine, this meeting seated a 12-member panel with no financial or career interest in the field of HBV research to formulate a statement aimed to widely disseminate strong, evidence-based recommendations for general practice. A report based on a systemic literature review was submitted by the Minnesota Evidence-based Practice Center to the panel, and leading HBV experts provided 1-1/2 days of presentations on the topic. The evidence report, meeting webcasts, and the draft consensus statement can be accessed at: www.consensus.nih.gov/2008/2008HepatitisBCDC120main.htm.

The data available are insufficient to provide patients, clinicians, researchers, and policymakers with high-quality information with which to make accurate prognostic and treatment decisions.
—Evidence Report/Technology Assessment No. 174, *Management of Chronic Hepatitis B*

The lack of clear clinical guidance creates a potential danger to patients.

Although the verdict rendered by the evidence report came as no surprise to people who follow HBV research, the blunt assessment on the current state of research data in HBV clinical management is no less sobering. The lack of clear clinical guidance creates a potential danger to patients that is not merely theoretical. For example, many people with HBV remained on lamivudine monotherapy for years in the belief that even suboptimal viral suppression could improve long-term outcomes. Eventually, data emerged showing that cross-resistance rendered subsequently approved drugs less effective, leaving many with fewer treatment options than if they had waited or switched to a combination therapy approach.

To be fair, the decade-long, fluctuating, and mostly silent and complex disease progression in chronic HBV presents a very difficult challenge for research measuring long-term clinical outcomes such as those of liver cirrhosis and cancer. Studies with the duration, size, and diverse treatment strategies required to fully answer these questions would be very expensive. Such large investments are unlikely to be made by the private sector, which has only sponsored small trials with short follow-up periods intended primarily for drug approval or for increasing market share after approval has been obtained.

Public financing for HBV research recently received a boost with the establishment of a national HBV clinical trials network. But with a first-year budget of only $3 million to be shared among 13 trial sites (and an annual $7 million in each of the following seven years) its funding is woefully insufficient to develop the definitive treatment guidance that is needed: long-term clinical outcomes comparing people who start treatment with people who wait; the safety and duration of benefit while off treatment; improved understanding of different disease progression patterns in people infected at birth versus those infected in adulthood and in those with different genotypes; identification of more accurate biomarkers for disease progression and reactivation; and the establishment of an HBV replicon system to speed identification of new drug targets.

What's more, the argument for increasing federal investment in HBV research is seriously hampered by the lack of visible demand. There is still no national chronic HBV surveillance program, and the recent CDC recommendation to increase chronic HBV screening came with no additional funding. A vicious cycle created by this data void is what confronts people living with HBV in need of treatment. With no compelling evidence to back up the need for a public assistance program like the Ryan White CARE Act and AIDS Drug Assistance Program, HBV advocates face a major challenge ahead. One hopeful approach would be to support the new administration's healthcare reform proposal that could increase affordable insurance coverage and eliminate exclusions based on preexisting conditions.

It is clear that the field of HBV research can benefit with the involvement of more advocates. If the paucity of new data on HBV at a recent major medical conference on liver disease in San Francisco is any indication, people living with chronic HBV and their clinicians will continue to struggle with making treatment decisions for years to come. ●

International Health Partnership
Just Another Initiative?

Despite the constant uphill battle in getting its issues on the table and our concerns heard, civil society recognizes that the International Health Partnership presents opportunities.

BY SUE PEREZ

Launched in September 2007 by UK Prime Minister Gordon Brown, the International Health Partnership and related initiatives (IHP+) is the newest invention by a collective of major international donors including several high-income country governments, the World Bank and UN agencies aimed at helping developing countries achieve the health-related Millennium Development Goals (MDGs), which include eradicating hunger; reducing child mortality; improving maternal health; and combating AIDS, tuberculosis, and malaria.

The IHP+ was not designed to create anything new but to make aid more effective and efficient. Improved donor coordination or "harmonization and alignment" is touted as a means to make lives easier for ministries of finance and ministries of health in developing countries, which are encouraged to set terms on how they want donors to behave—that is, to provide aid based on countries' individual budget cycles and priorities, to allow countries to report on expenditures in one format acceptable to all donors, host fewer donor missions, and develop one comprehensive national health plan.

AIDS activists working on global health, along with their allies in other advocacy fields, have emphasized that better donor coordination alone will not be enough to achieve the health MDGs. Greatly increased donor funding for health in developing countries will be crucial. Ethiopia, the first IHP+ partner country to develop budget estimates for its comprehensive health plan, identified a significant funding gap of up to $2.8 billion between 2008 and 2010. However, Ethiopia has yet to see any major new money to fill this gap.

What worries AIDS and TB activists the most is that the IHP+ is driven by donors who have directed their attention increasingly to the sector wide health systems corner. AIDS and TB activists readily admit there is a need to increase investment in health systems because any health interventions, including those for HIV/AIDS and TB, cannot be sustained without functioning health systems. However, with limited resources, donors will have to make choices about where to put their money, and this could result in the cutting of existing funding for AIDS, TB, and malaria, and moving money to general "[health] sector wide approaches" (or SWAps) that, as a result of its record, have gained a poor reputation for preserving high-quality priority-disease programs. For example, in the 1980s and '90s, several African countries dismantled their TB programs as a result of donor-supported SWAps and macroeconomic policies advised by the International Monetary Fund (IMF), contributing to the disastrous upsurge in TB cases that accompanied the explosive emergence of the HIV pandemic. AIDS and TB activists have strongly warned the IHP+ partners about the potential for collateral damage to disease-specific programs as a result of shifting money to health systems strengthening. The UK government's announcement in June 2008 of its new HIV/AIDS strategy, which committed £6 billion for "health systems and services" between 2008 and 2015 yet did not commit any specified funding amount for HIV/AIDS-specific interventions, is a prime example of the threat this shift poses to achieving universal access to treatment, prevention, care, and support for those infected with HIV and TB.

Activists have also targeted the lack of meaningful involvement of civil society in the IHP+, especially at the national level. Despite lip service, activists and civil society were not offered seats at the table of the IHP+ oversight group. The voices of TAG and other strong activists had to advocate loudly to gain meaningful participation. This was a bit of a feat considering that the table hosts the World Bank; WHO; UNFPA; UNAIDS; UNICEF; the Global Alliance for Vaccines and Immunizations; the Global Fund to Fight AIDS, Tuberculosis and Malaria; and the Bill and Melinda Gates Foundation. Not all IHP+ partners have historically welcomed civil society participation. TAG has been serving as one of two civil society representatives to the IHP+ oversight group, and has played a central role in voicing against what civil society views as a "robbing Peter to pay Paul" situation in terms of shifting resources to health systems strengthening. TAG and others have also loudly spoken out against tokenistic civil society involvement in IHP+ processes at all levels and against the resistance by IHP+ partners to address harmful policies by the IMF.

The IHP+ heard our message about civil society engagement loud and clear. In May 2008, the World Bank and WHO organized an IHP+ civil society forum that brought together members of civil society groups from nearly all 14 IHP+ developing country partners and donor and UN agency representatives. Activists and civil society used the opportunity to air all their questions, concerns, and warnings to staff from donors and UN agencies present. Several of TAG's African and Asian partners participated. At the meeting, civil society presented its three key principles of the IHP+ as follows: (1) comprehensive primary health care for all; (2) governments must pay their fair share; (3) people's voices must be heard. These principles inspired a show of unity among global health advocates. A declaration outlining these principles was signed by over 100 health systems, child and maternal health, and AIDS and TB advocates.

Despite the constant uphill battle in getting its issues on the table and our concerns heard, civil society recognizes that the IHP+ presents opportunities. Activists see the potential of the IHP+ to build a global health movement that unites rather than divides civil society in the either/or categories of health systems or priority disease programs for AIDS, TB, and malaria. The IHP+

Continued on page 9

TAG's TB/HIV Project
International Advocacy Update

Presentations from TAG's recent meeting on universal access to TB and HIV treatment, care, and prevention as well as TAG's *Funding Trends in TB R&D 2005–2007: A Preliminary Report*, are available at www.treatmentactiongroup.org.

BY CLAIRE WINGFIELD

The International Union against Tuberculosis and Lung Disease (IUATLD) held its annual World Conference on Lung Health in Paris, October 16–20. The conference is the largest gathering of TB researchers, advocates, policy makers, service providers, and funders, and provides one of few opportunities for these key stakeholders to meet face-to-face each year. Prior to the start of the conference, TAG held a satellite meeting titled "TB/HIV Programs: Working Together to Achieve Universal Access to HIV and TB Prevention, Care, and Treatment." The theme of the satellite meeting was TB and HIV program collaboration as a key strategy in achieving universal access for TB/HIV services, with a focus on sharing lessons learned and identifying key opportunities to encourage synergy between the two programs and other key stakeholders. TAG's partners in organizing the daylong meeting were the Stop TB Partnership (a global membership organization of over 700 institutions and individuals concerned about TB), and AIDES (an AIDS nongovernmental organization providing direct services and policy advocacy in France and Francophone Africa).

Approximately 70 participants attended the satellite meeting, including national TB and AIDS control program personnel, researchers, policy makers, funders, and activists. The participation of representatives from national HIV programs at the meeting was significant, as they historically have not participated in TB conferences. In fact, at the urging of TAG and other partners, the IUATLD invited and sponsored ten national AIDS control managers from TB/HIV high-burden countries to attend the conference. The satellite session was an opportunity for staff from the HIV and TB programs, which often work in parallel, to discuss challenges to addressing TB/HIV coinfection and strategize on how to partner more effectively and maximize resources.

The aim of the satellite meeting was to highlight the impact that TB/HIV coinfection is having on countries trying to achieve global TB and HIV targets, and therefore the need for TB and HIV programs and other key stakeholders to work more collaboratively in providing comprehensive and integrated TB/HIV services. Four panels explored the progress made toward universal access to TB/HIV prevention, care, and treatment at country and global levels and shared successful models of collaboration and community engagement. Panelists representing different sectors shared their experiences and discussants provided a critical analysis of the presentations. The panel discussions focused on the impact of TB/HIV on HIV universal access and Global Plan goals; reducing the burden of HIV among people with TB; reducing the burden of TB among people with HIV; and resources needed to facilitate collaboration to achieve universal access to TB/HIV services.

In addition to the satellite meeting, TAG, in partnership with the Consortium to Respond Effectively to the AIDS and Tuberculosis Epidemic (CREATE), a leading TB research consortium, sponsored a press conference in order to highlight the need for newer and better tools to prevent, diagnose, and treat TB as well as call for more resources to encourage and support the development of these new tools. The panel of speakers included Drs. Françoise Barré-Sinoussi of the Pasteur Institute, Richard Chaisson of CREATE/The Johns Hopkins Medical Center, Mel Spiegelman of the Global Alliance for TB Drugs, Paul Nunn of the Stop TB Department of the WHO, and TAG's executive director, Mark Harrington.

At the press conference TAG released *Funding Trends in TB R&D 2005–2007: A Preliminary Report*, which found that if funding for TB research continued at its current rate, less than half of the $9 billion recommended by *The Global Plan to Stop TB: 2006–2015* will be spent on TB research and development by 2015. Mark Harrington warned that "after documenting TB research investments for 2005 through 2007—the last three years for which complete data are available—we can say that promises made by world governments and the private sector to supply the needed TB investment specified in The Global Plan are not being kept." Dr. Barré-Sinoussi, who shared the 2008 Nobel Prize in Medicine for discovering HIV, emphasized that "expanded, accelerated research to combat tuberculosis—including HIV-related TB—is a key part of the world's struggle against both diseases." ●

IHP+ (cont.)

is an opportunity to change the donor-developing country government dynamic where assessment, development, planning, and budgeting for the health sector typically exclude civil society input. These plans then end up as government plans and not "country plans" and thus often leave out specific strategies for reaching poor, vulnerable, and marginalized communities.

The IHP+ also presents an opportunity to push forward efforts to reform the role of the IMF in health and development. Numerous studies have shown that IMF policies create caps on developing country public sector budgets—including health budgets. The impact of IMF policies is a key factor that has severely hindered African countries from reaching the Abuja Declaration target of allocating 15% of total budget to health.

With all of the challenges and opportunities, activists have a lot of work to do.

As we head into year two of the IHP+, the jury is out as to whether the IHP+ is just another donor-motivated initiative or one that truly changes things for the better. AIDS and TB activists will continue to keep a watchful eye on the IHP+ and lead the way in making sure that other voices are heard. ●

Bacteria (cont.)

Lessons from Mice

In support of the idea that a lack of CD4 T cells can cause microbial translocation, Marchetti and colleagues cite a basic immunology study from way back in 1980. The paper reports that microbial translocation occurs in mice bred to lack a thymus (an organ that essentially serves as a T-cell training camp), and is reduced when these mice receive thymic grafts (which restore their ability to make naive T cells). Complementary findings were reported in a more recent mouse study published by the journal *PNAS* in June 2008. Christine Bourgeois and colleagues from Brigitta Stockinger's laboratory in London reported that blocking the export of new naive T cells from the thymus led to microbial translocation, which in turn exacerbated the depletion of existing naive T cells by causing immune activation. Naive CD4 T cells were particularly sensitive to activation in this setting, leading to a skewing of the CD4/CD8 ratio. The researchers note the similarity with other settings in which naive T-cell depletion is observed, such as aging and HIV infection, and conclude that "continued replenishment with cells from the thymus seems to be required to maintain efficient gut mucosal defense."

Taken together, these data may suggest that the slow, progressive depletion of naive CD4 T cells that occurs over the course of HIV infection could also contribute to microbial translocation. Under this scenario, even complete HIV suppression might be unable to prevent persistent immune activation if naive CD4 T-cell reconstitution is poor. Aging would also represent another complicating factor, as thymus function declines dramatically in adulthood and naive T-cell output slows to a relative trickle by the sixth decade of life.

One means to address whether the data from basic immunology studies have any relevance to humans (which is extremely uncertain, given the large differences between mice and people) may be through studies of immune-based therapies with the potential to accelerate naive T-cell reconstitution. Interleukin-7 is one such candidate and phase I trials are ongoing. A pilot study published by Laura Napolitano in the *Journal of Clinical Investigation* has shown that human growth hormone (considered inappropriate for further development due to potential toxicity) can increase naive T cell levels in people with HIV and it also significantly decreased CD38 expression on CD4 and CD8 T cells. A growth hormone derivative, tesamorelin, is now being developed as a treatment for lipodystrophy but the immunological effects have yet to be evaluated.

Hopefully, further research with these types of interventions will help answer the question of whether naive T-cell reconstitution can contribute to reducing microbial translocation and immune activation. Since poor immune reconstitution despite ART is also associated with a significantly elevated risk of clinical illness and death, the issue is not just academic; it is possible that a successful immune-based therapy could produce measurable health benefits. ●

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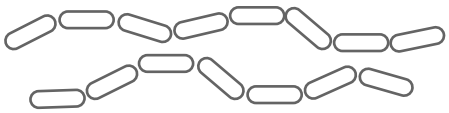

Fifty Years of AIDS Treatment
1981–2031

A speculative history of HIV treatment presented at the PATH aids2031 meeting "Discovery and Innovation for HIV/AIDS" held in Seattle, November 18, 2008.

BY BOB HUFF

1981
First reports of disease later known as AIDS; 100% fatality feared.
1983
HIV identified as cause of AIDS; first treatment attempts fail.
1985
AIDS vaccine said likely within two years.
1987
AZT, first anti-HIV drug, approved.
1988
AIDS activists surround FDA headquarters in Rockville, Maryland, demanding faster drug development.
1996
Triple combination treatment "cocktail" with new protease inhibitors dramatically reduces HIV in blood.
1998
Death rate from AIDS plummets in United States and Europe.
1997
Body fat abnormalities, toxicities appear in people taking HIV drugs.
Experts expect AIDS vaccine within 5–8 years.
2000
Treatment Action Campaign (TAC) marches at International AIDS Conference in South Africa to demand HIV drugs for developing world.
U.S. guidelines call for HIV treatment when CD4 cell counts reach 250 cells/mm^3; stavudine widely used in United States.
2001
Prices of Indian-made generic HIV drugs drop; treatment in developing world becomes feasible.
Developing world guidelines call for HIV treatment when CD4 cell counts reach 200 cells/mm^3.
Primary HIV drug regimen in the developing-world contains stavudine, lamivudine, and nevirapine.
2004
Stavudine linked to body fat problems; dropped from U.S. guidelines. Tenofovir now preferred in the developed world; cost is prohibitive elsewhere.
2006
Goal of universal access to HIV treatment by 2015 voiced by international community.
HIV vaccine predicted within 5 to 8 years.
2007
Prolific period of HIV drug development ends with approval of first integrase inhibitor and first CCR5 antagonist; 26 HIV drugs approved for use in the United States.
Highly effective and safe first-line and salvage HIV regimens available to most patients in the developed world.
U.S. guidelines call for starting HIV treatment when CD4 cell counts reach 350 cells/mm^3.
Developing world continues to use stavudine and start treatment at 200 CD4 cells/mm^3.
2008
Financial markets shocked; Barak Obama elected U.S. president.
2009–2016
Depression. Worldwide economic collapse hits emerging economies and developing countries especially hard. Trade virtually stops in Africa; people leave cities to seek food. Three generic drug makers exit the HIV treatment field.
Western governments struggle to spend on foreign aid. U.S. president Obama spearheads global health safety net funded by 2% of world GDP.
Funding for Global Fund and PEPFAR HIV drugs continues but treatment rarely delivered outside of cities. Progress toward universal HIV drug access halts. Treatment money stable but absorbed by switch to tenofovir as fewer patients are treated.
2013
HIV prevalence in Africa drops as transmission declines due to restricted trade and mobility and as AIDS deaths increase.
AIDS activists march in world capitals demanding new drive to universal HIV treatment access.
2015
HIV drug development continues slowly in developed world. Next-generation drugs in existing classes approved featuring low doses, long half-lives, and virtually no toxicity.
2016
U.S. guidelines recommend new 50mg, once-daily, fixed-dose-regimen tablet of integrase inhibitor plus a protease inhibitor. The compact combination is licensed widely to generic makers; low-cost regimen quickly adopted in developing world; treatment access improves.
New guidelines recommend treating HIV infection without regard for CD4 count: treat when diagnosed.
Novel U.S. government campaign pays people to take HIV test; 250,000 newly diagnosed go on treatment; transmission rates drop.
Experts predict HIV vaccine within 5 to 8 years.
2017
Once-monthly HIV drug regimen in subcutaneous formulation approved; widely adopted in prisons and for nonadherent patients.
2020
Revolutionary, monthly combination anti-HIV transdermal patch introduced. Developed by three Indian generic companies holding new patch technologies; best ideas combined into one product with intellectual property rights assigned to "patent pool." Breakthrough technology attracts drug patent holders to participate. New HIV patch costs $25/year; safe; sold over the counter. Artists create colorful and trendy patch designs. Patch and drugs biodegradable.
Human and economic health improving worldwide as economies surge.
2021
Chinese company develops broad spectrum microbicide based on natural product; safe for vaginal and anal mucosa. Product tastes great; successfully marketed as soft drink; no stigma when used as microbicide. Wide market distribution achieved at low cost.
2024
Worldwide HIV prevalence dropping as treatment rates increase; on track to become "like polio" by 2056.
"Cure Pak" studied in large clinical trials; regimen delivered as blister pack containing 60 days of anti-HIV drugs, 7 days of drugs to activate latent immune cells, and then another 60 days of HIV drugs. One-year, drug-free remission achieved in 40% of participants.
2026
U.S. president Michelle Obama announces breakthrough antiaging technology derived from HIV pathogenesis research.
First HIV vif protein inhibitors enter human trials.
2030
Nonpathogenic HIV strain found integrated into germline of extended family in Central Africa.
2031
First experimental nanomachines "walk" DNA in yeast to locate and edit out HIV sequences.
Implantable nanoarray sensors projected to provide real-time telemetry of gene and protein expression in human immune tissue in vivo; hopes increase that correlates of immune protection can be found.
Experts predict HIV vaccine within 5 to 8 years.

TAG NEW WAYS TO CONTRIBUTE

Supporting TAG is a wise investment in AIDS treatment advocacy. With a small but well-organized and highly respected staff of professionals, every donation to TAG brings us one step closer toward better treatments, a vaccine, and a cure for AIDS.

There are several ways you can support TAG today!

Make a tax deductible gift now
by credit card using our secure website (www.treatmentactiongroup.org) or by calling Joe McConnell at TAG at 212.253.7922 to request a donation envelope.

Celebrate!
Expand your support for TAG by asking your friends and family to make a donation in your honor to celebrate your birthday, anniversary, or the holidays. An acknowledgment will be sent to the donor, as well as to you informing you of the gift made in your honor. Please call TAG at 212.253.7922 to request that materials be sent to friends and family.

Support TAG's Research in Action Awards
Each December, TAG's Research in Action Awards event honors some of the most important scientists, artists, celebrities, and activists working for better treatments, a vaccine, and a cure for AIDS. Past honorees and presenters have included New York State Senator Tom Duane, director and artist John Waters, award-winning playwright Terrence McNally, actor Nathan Lane, and stage and screen actress Kathleen Turner, among many other scientists and dedicated AIDS activists. Join us this December!

Does your company have a matching gifts program?
If so, you can double or even triple the donation you make to TAG. If your company offers a matching gifts program, please complete its matching gift form and send it in with your donation to TAG.

Make a gift of stock to TAG
Gifts of stock benefit TAG and the donor. The donor who purchased the stock at a lower price receives the tax deductible benefit of the stock's price on the day it is transferred to TAG.

For more ways to support TAG, please visit our website at www.treatmentactiongroup.org or contact Joe McConnell at TAG at 212.253.7922.

TAG BE INVOLVED

About TAG

Treatment Action Group is an independent AIDS research and policy think tank fighting for better treatment, a vaccine, and a cure for AIDS. TAG works to ensure that all people with HIV receive lifesaving treatment, care, and information. We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions. TAG catalyzes open collective action by all affected communities, scientists, and policy makers to end AIDS.

Program areas include antiretroviral treatments, basic science, vaccines, prevention, hepatitis, and tuberculosis.

Join TAG's Board

TAG is always seeking new board members. If you are looking for a great place to invest your time and talents, please call Barbara Hughes, TAG board president, to learn more about board opportunities with TAG.

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