TAG line

Treatment Action Group

VOLUME 12 ISSUE 2 DECEMBER 2006

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Treatment Action Group
611 Broadway, Suite 608, New York, NY 10012-2608
Tel. (212) 253-7922 Facs. (212) 253-7923
E-mail: tagnyc@verizon.net
www.treatmentactiongroup.org

Activist Chides TB Congress for Complacency in Facing Drug Resistance

By Theo Smart
Aidsmap.com

"You are more invested in the DOTS model—which has failed [to contain] multidrug-resistant TB (MDR-TB) and which is now breeding extensively drug-resistant (XDR) TB—than you are in saving lives," Mark Harrington, Executive Director for the Treatment Action Group (TAG) told TB (tuberculosis) experts attending a symposium held by the Stop TB Partnership of the World Health Organization (WHO). The symposium occurred a day before the 37th Union World Conference on Lung Health, which took place in Paris from November 1–4, 2006. Harrington challenged the TB experts to put the interests of people with TB first, and to act aggressively to put the necessary infrastructure in place to diagnose MDR-TB and XDR-TB.

"There's a failure of leadership at all levels."

Shift to Community-Based Approach

Directly observed therapy (DOTS) is a public health-based approach to TB control which focuses primarily on preventing the spread of TB by screening for people with active infectious pulmonary TB (as detected by smear microscopy), and then engaging healthcare workers to directly observe the administration of treatment to the person with infectious TB until the infection is cured.

Activists have accused the DOTS approach of treating people with TB more like vectors of disease than human beings—stigmatizing them, and thereby greatly undermining any potential for empowerment of TB patients and the development of a TB activist community. Furthermore, many believe the model virtually ignores most people with HIV-related TB, who often have either extrapulmonary or smear-negative TB, because those conditions are generally non-infectious (though no less fatal), and people with multidrug-resistant TB (MDR-TB) because they were too difficult to treat. As a result, for years people with MDR-TB and smear-negative HIV-related TB were neglected and essentially left to die.

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But in the face of the failure of the DOTS approach to contain TB in countries with a high burden of HIV, the TB world has in recent years been attempting to revamp its policies and engage the TB- and HIV-affected communities. With the assistance of HIV/AIDS activists, they have also adopted more of an activist approach towards getting the necessary funding to develop new tools to diagnose, prevent and treat TB. This new policy direction is laid out in the recent Global Plan to Stop TB 2006–2015.

However, according to a recent policy report from TAG (*Tuberculosis Research & Development: A Critical Analysis*), these efforts don't go nearly far enough. Although the Global Plan estimates a funding need for $9 billion in research on new TB tools including new drugs, diagnostics and vaccines, according to the TAG analysis, the Global Plan did not budget for the basic science, infrastructure development, and operational research necessary to provide a foundation for and validate these new TB tools. "The Global Plan does not specifically call for greater investment in basic science, which underpins all discovery efforts, nor does it fully account for the operational research needed to integrate new tools into health care systems," the authors wrote. TAG estimates that investment in these areas needs to increase at least five-fold to approximately $950 million per year.

"We should be more ambitious about asking for what we need."

Is the TB World Up for Handling the XDR-TB Crisis?

According to Harrington, the emerging crisis of extensively drug-resistant TB highlights some of the other shortcomings of the Global Plan—and the tepid response on the part of the TB research and treatment community in confronting MDR-TB over the years.

"Now the reason why I am saying to many of you that you really believe in DOTS and you don't believe in saving the lives of people with MDR-TB is because it's not in your Global Plan to treat 75% of the people who are going to get MDR-TB in the next ten years," he said. "And it's not in the Global Plan to scale up the labs to even do a good job with [smear microscopy]; and it's not in the plan to scale up infection control; and it's not in the plan to scale up to universal [drug sensitivity testing] and culture; and it's not in the plan to put up enough money for research and development. So even though you guys all work in TB and you all think you are trying to save lives, some of you are addicted to the DOTS strategy—which is a public health strategy and is not a patient-centered strategy—and it condemns hundreds of thousands of people a year to death."

Many resource-limited settings confronted by TB/HIV and the potential for high mortality from MDR-TB and XDR-TB lack the basic laboratory infrastructure to perform drug sensitivity testing, culture and diagnose TB in a timely manner. To Harrington, this is particularly galling: "As an AIDS activist I'm here to tell you that this is unacceptable, and it's a failure of leadership at all levels," he said. "I want you all to become activists and radicals... and call for universal access to high quality first-line and second-line treatment and cure for everybody that gets TB—adult and child, MDR and drug susceptible, TB HIV-positive and TB HIV-negative. I think that universal access to all these TB interventions by 2010 is a non-negotiable demand, and you all need to go back and rewrite your Global Plan to get us to universal access by 2010. To do anything less is to let down the millions of people that you claim to serve and whose lives you're being paid to save."

Javid Syed, WHO Community Representative and TB/HIV Project Director for TAG put the issue somewhat more gently: "Our main goal has been to look at how we can apply some of the lessons learned in the HIV world and apply them to the TB world. One of our main messages is that the TB world is really humble in what it asks for, and it quite often never asks for what it needs. Part of our message is that we should really be more ambitious about asking for what we need."

The original article appeared on www.aidsmap.com, November 2, 2006.

Tuberculosis Research & Development: A Critical Analysis

TAG interviewed 100 institutions and documented the top 40 investors in TB R&D in 2005. Results highlighted in the report showed that new tools including diagnostics, drugs and vaccines received combined funding of $206 million in 2005-diagnostics, $16 million; drugs, $120 million; and vaccines, $70 million. At this rate, only $2 billion will be available over the next decade, whereas the Global Plan to Stop TB 2006–2015 estimates that $9 billion will be needed, revealing a new TB tools funding gap of $7 billion. Basic science and operational research received $94 million and $50 million, respectively, but there are no global targets with which to compare the investments in basic and operational research.

To improve upon decades old technology and match urgency with need, Treatment Action Group demands donors of TB R&D worldwide—including G8 and developing countries—increase their investment five-fold, from less than $400 million per year to $2 billion per year, with $1.05 billion directed towards new tools research and $950 million directed towards basic science, infrastructure development, and operational research each year, for a total of $20 billion in TB R&D over the coming decade.

Full report available at www.treatmentactiongroup.org

How We Treat TB Today

A Talk with Gavin Churchyard

By Mark Harrington

Professor Gavin Churchyard is the director of the Aurum Institute for Health Research, which provides health care services to many mining companies in South Africa but is also an independent health research center conducting a number of important clinical trials, including the Thibela-TB trial of isoniazid preventive therapy (IPT) in 35,000 mine workers, funded by the CREATE consortium with support from the Bill & Melinda Gates Foundation, and a pivotal study of a new HIV vaccine sponsored by the U.S. National Institutes of Health and Merck & Co. Dr. Churchyard has been conducting research and providing health care to South African miners for over a decade and is a world-respected expert on TB. I spoke to him during a meeting held at Kwa Maritane, Pilanesberg, South Africa, from 18–20 September, involving researchers from Brazil, the U.K., the U.S., Zambia, and South Africa who are conducting three very large studies to better understand how to control HIV-associated TB infections.

Dr. Churchyard: The extent of multi-drug resistant (MDR), highly-drug resistant, and extensively drug resistant (XDR) TB in the mining industry is unknown at this time. Some of the MDR TB which we know exists in the mines is likely to be XDR TB—we don't yet know how much. The overall rate of MDR in the mining industry is 2–3% (1% in people with first TB infection and 4% in TB retreatment cases). The industry needs to implement surveillance strategies to quantify the magnitude of the MDR/XDR epidemic, and strengthen and intensify infectious control policies at all levels.

Individuals should be urged to seek testing to know their HIV status, offered antiretrovirals early, and communities need intensified awareness and education about TB symptoms so they can seek out diagnosis and treatment for TB as early as possible.

The health system in the mines incorporates high-quality diagnostic and treatment facilities which can diagnose TB rapidly, detect whether it is drug-resistant, and apply the best treatment regimen which would be appropriate for the resistant strain, if MDR or XDR. However remember that 97% of TB cases are curable with six months of proven effective and safe combination therapy. TB can also be prevented with six to nine months of isoniazid (INH) preventive therapy (IPT), which has proved to work in many countries in over forty years of research and is effective among people with HIV.

It is particularly urgent for HIV-infected persons with TB symptoms to be rapidly diagnosed as the XDR strain rapidly kills people with HIV (within days).

Everyone must learn, understand, and implement effective infection control procedures including light, ventilation, identifying coughing patients and having special places for them in waiting rooms and clinics, expedited screening, educating health care workers, patients, community members, political leaders, and the media about how to prevent TB transmission, how to seek care for TB symptoms, how to diagnose, treat, and cure TB. By far most TB cases are sensitive and respond to therapy.

Individuals with TB including XDR-TB are human beings with human rights. We must treat all people with TB with respect, preserve their dignity, and save their lives. There is no role for stigma and discrimination in managing TB. By explaining the importance of adherence to TB treatment, we can help support individuals with the disease to achieve treatment success and save their lives.

Some individuals with XDR TB may be treated in single bed hospital rooms. They are not pariahs. Wearing a mask can prevent transmission even in the weeks when they may still be shedding TB bacteria by coughing. Regular TB drugs eliminate infectiousness after two weeks. There is a simple test (the sputum smear microscope acid-fast bacilli test) which can determine whether someone is still infectious. Most people stop being infectious after treatment is initiated. With MDR and XDR TB the time to loss of infectiousness is more variable. Treatment takes longer and involves more drugs, with greater side effects. However many cases of MDR TB can be cured if caught in time. XDR TB can be treated but it is not yet clear whether it can be cured without new drugs still in early phases of development. This terrible outbreak of XDR TB demonstrates how critical it is to assure access to high-quality TB services for all, and to accelerate and intensify research to discover new drugs to cure MDR and XDR TB.

TB Transmission in Healthcare Settings

By Theo Smart
Aidsmap.com

In all the news and hype about the cases of extensively drug resistant tuberculosis (XDR-TB) in KwaZulu Natal, South Africa, there has been surprisingly little discussion about how and where many of the people acquired the XDR-TB infections.

"The evidence, I think, clearly points to nosocomial transmission of a very lethal organism," said Dr. Gerald Friedland of Yale University during a symposium on Infection Control at the recent 37th World Union on Lung Health Conference in Paris. Dr. Friedland collaborates with the researchers in KwaZulu Natal, South Africa who reported the cases of XDR. (Nosocomial means an infection or disorder acquired in hospital).

Dr. Anthony Moll was the clinician at the 350-bed district hospital in Tugela Ferry, South Africa, who first detected what would turn out to be XDR-TB in a subset of his TB patients. The hospital serves a rural district with a very high prevalence of TB: a case rate of 800 to 1,000 per 100,000 individuals, and 70–80% of the cases are HIV co-infected.

Dr. Moll was running a novel TB/HIV integration study offering treatment and care for both diseases in coinfected patients (with family members offering adherence support) in which the majority of patients were doing extremely well—but he noticed an unusually high and rapid mortality rate in a subset of 14 patients. Ten of these were found to have MDR- and eventually XDR-TB (6 in newly treated patients and 4 in patients who had successfully completed a course of treatment).

"The rate of MDR in newly treated cases in the study was 9%" said Dr. Friedland. This was four times the rate of MDR-TB that had been reported in the last prevalence survey five years previously.

So they decided to perform a local clinical and mycobacterial survey (with drug sensitivity testing) which included three groups: 1) all the recent treatment failures and retreatment cases, 2) the in-patients in TB wards and 3) TB suspects presenting to the district hospital with TB symptoms. The survey included a total of 1539 patients, 544 of whom were culture positive, 221 (41%) of whom had MDR-TB and 53 of whom were XDR-TB.

Although MDR-TB appeared to be endemic in the area—and XDR-TB is a natural by-product of inadequately diagnosed and treated MDR-TB—26 (55%) of the 53 people identified with XDR-TB turned out never to have been treated for TB before.

A chart review, which included demographics, prior TB, and prior hospital admissions, was performed for the people with XDR-TB but failed to reveal anything that linked all these subjects together, except that two-thirds of them had been hospitalized within the past two years—and all 53 had used the same district hospital on either an in- or outpatient basis. Also telling was the fact that contact tracing identified no additional cases in the community, and DNA fingerprinting suggested that 85% of the isolates were genetically similar.

"Looking at previous TB treatments and previous hospitalization, putting all of that together gave us the idea that we were looking at nosocomial spread of XDR-TB," said Dr. Moll.

Transmission To People With HIV

But what's particularly distressing is that the hospital at Tugela Ferry was the very first in the province to offer antiretroviral therapy, and thus it has served as a magnet to people with HIV in the area. Forty-four of the 53 were documented as HIV-positive and would have been receiving their HIV care from the hospital.

"Patients are congregating for ARVs in hospitals where TB control has been neglected."

"This whole issue obviously raises the problem of tuberculosis transmission in congregate settings in hospitals," said Dr. Kevin de Cock, Director of the WHO Department of HIV/AIDS, in another session of the conference. "We are congregating patients for ARV services in hospitals where infection control has been neglected over the years."

"Transmission of MDR and XDR-TB really must be addressed to further improve survival for HIV co-infected patients," said Dr. Friedland. "I would say quite ominously that in high-prevalence areas, the success of both antiretroviral therapy and TB-DOTS programs is really threatened by the presence of MDR and XDR TB."

Indeed if people perceive that waiting rooms and in-patient facilities are dangerous places (and in many situations, they clearly are), it could significantly impact on health-seeking behavior.

Excerpted from a report in HIV & AIDS Treatment in Practice (HATIP) *#79, December 19, 2006.*

Gut Reactions

By Richard Jefferys

The biggest obstacle to understanding how HIV causes immune damage is the complexity of the human immune system, a vast collection of different cells and tissues that typically work together in concert to protect against disease. HIV infects CD4 T cells—a central coordinator of the immune response—and causes a gradual depletion of these cells from both the peripheral blood and lymphoid tissue, along with a spreading dysfunction among the remaining CD4 T cell population. The precise mechanisms governing the loss and dysfunction of CD4 T cells, particularly the relative contributions of direct and indirect effects of HIV replication, continue to be hotly disputed among scientists. These disputes persist because immunologists do not fully understand how the huge pool of CD4 T cells in humans (numbering in the billions) is generated and maintained under normal conditions. It is known, however, that a majority of CD4 T cells reside not in the circulating blood but in lymphoid tissue throughout the body, including the gut.

Over the past few years, there has been renewed interest in studying the potential impact of HIV infection on CD4 T cells in the gut in the hopes of answering outstanding questions about HIV pathogenesis. Some researchers, particularly a group at the National Institutes of Health Vaccine Research Center (VRC) led by Daniel Douek, have generated data suggesting HIV causes a rapid, severe depletion of CD4 T cells from the gut-associated lymphoid tissue (GALT), leading to the theory that this depletion sets the stage for the eventual development of severe immunodeficiency and AIDS. In its most dramatic formulation, this theory holds that people lose half their memory CD4 T cells within weeks of becoming infected. (Douek's research group has very recently published data suggesting that this loss of CD4 T cells actually allows commensal "friendly" bacteria [which normally aid digestion] to leak from the gut into the circulation, and this causes the systemic immune activation that is associated with HIV infection [see Update page 6].)

However, not all researchers accept the CD4 catastrophe theory; several have published alternative interpretations of the data and argue that the importance of gut CD4 T cell depletion has been overstated. Among this camp of researchers are Zvi Grossman, Martin Meier Schellersheim, Bill Paul, and Louis Picker who argue that the CD4 T cells lost from the GALT are highly activated short-lived effector CD4 T cells and not the long-lived memory CD4 T cells that are essential for protection against opportunistic infections. They point out that long-lived (also known as "central") memory CD4 T cells are eroded far more slowly over the course of disease. This point of view has recently been dramatically bolstered by the revelation that sooty mangabeys infected with SIV, a monkey form of HIV, show a similar gut "depletion" of CD4 T cells, despite the fact that they almost never progress to immunodeficiency.

Australian immunologists Anthony Kelleher and John Zaunders have also argued that the GALT data are less clear-cut than it may at first appear, citing studies that appear inconsistent with Douek's hypothesis and echoing the notion that effector CD4 T cells appear most depleted and that the impact on memory CD4 T cells is far less clear.

As it stands, only additional research can resolve these differences of opinion. But as the debates continue, it's helpful to review the data and take a look at how theories about the importance of GALT originated.

"The pursuit of science is not immune to fads and fashions."

The Intestinal Terrain

The surface area of the human intestine, which is lined with folds and creases, villi and crypts, is almost inconceivably enormous—larger than a football field, were it all flattened out. The gut begins with the small intestine, which has three parts: the duodenum, jejunum and ileum. This is followed by the large intestine, also subdivided into three parts: the caecum, colon and rectum. The entire intestinal tract contains lymphoid cells scattered throughout the intestinal epithelium (the cellular layer that makes up the surface of the intestine) and lamina propria (a thin layer of tissue beneath the epithelium containing capillaries and a lymph vessel).

There is also an additional layer of complexity: the GALT includes distinct immunological areas known as inductive and effector sites. As the name implies, inductive sites are where immune responses are initiated. It is here that antigen-presenting cells activate CD4 T cells, CD8 T cells and B cells. Effector sites are where these cells migrate subsequent to activation. The balance between inductive and effector sites varies somewhat in different locations in the intestine: in humans, the jejunum and the region of the ileum closest to it (the proximal ileum) possess relatively little inductive lymphoid tissue whereas the terminal ileum (closer to the colon) and colon contain both inductive and effector sites.

Early Studies in HIV

Scientific papers describing alterations in T cell subsets in the gut of HIV-infected individuals began appearing in the late 1980s. The common theme that emerged from this research was that the percentage of CD4 T cells was severely decreased while the percentage of CD8 T cells was elevated. Notably, results were similar regardless of the route of transmission.

A 1995 study that compared samples taken simultaneously from the duodenum and peripheral blood found that the decrease in the proportion of CD4 T cells in the duodenum was consistently more profound than that seen in the blood, even in people with asymptomatic infection. Further details emerged from a 1997 study by Donald Kotler's group which evaluated the extent of CD4 T cell depletion in the inductive versus effector sites of the rectal mucosa. These researchers found that the extent of depletion in the inductive sites was limited and more closely mirrored the peripheral blood; in contrast, CD4 T cells were dramatically reduced in the effector sites of the lamina propria. A logical hypothesis suggested by these data was that HIV's preference for replicating in activated CD4 T cells made effector sites in the GALT a particularly hospitable environment for the virus.

Depletion Theories Take Hold

In 2004, two studies were published simultaneously in the *Journal of Experimental Medicine*. One study, from Daniel Douek's laboratory, evaluated 14 people with HIV along with seven controls. The second study was conducted by Martin Markowitz's research group at the Aaron Diamond AIDS Research Center (ADARC) in New York and involved 27 people with HIV and 10 uninfected controls.

"Does HIV wreak an almost instantaneous blitzkrieg in the gut?"

The Markowitz study compared inductive and effector sites and reported that the former showed no absolute CD4 T cell depletion. At the effector sites, CD4 T cell depletion was more severe, with a mean CD4/CD8 ratio of 0.4 in the setting of HIV infection compared to 1.3 in HIV-negative controls.

Douek's research group also noted that a decline in CD4 T cell percentage does not necessarily equate with an absolute CD4 T cell decline and took pains to home in on CCR5-expressing memory CD4 T cells, which made up a dramatically smaller proportion of memory CD4 T cells in the GALT of HIV-infected study participants compared to controls.

Included in this report was a photograph from the ileum of an individual with acute infection, showing a complete absence of lymphoid tissue. This photo was subsequently shown by Douek during a plenary session of the 2005 Conference on Retroviruses and Opportunistic Infections (CROI 2005) (where he also offered his speculation regarding the role of commensal bacteria in causing immune activation in people with HIV); this single photo became emblematic of the guts-theory of HIV pathogenesis, which was widely reported by journalists at the conference.

Update: Leaking LPS

As this issue went to press, a paper appeared from Daniel Douek and colleagues reporting data which, the authors argue, further supports the model of HIV pathogenesis outlined in their Nature Immunology review. Douek's group had previously speculated that one pathogenic byproduct of HIV's impact on the gut might be to inappropriately allow bacterial byproducts into the bloodstream—a phenomenon known as "microbial translocation"—allowing them to stimulate runaway immune activation, ultimately leading to CD4 T cell loss and AIDS.

In the December 2006 issue of *Nature Medicine*, the researchers report that people with chronic HIV infection and AIDS—but not acute or early HIV infection—have higher levels of lipopolysaccharides (LPS) in their bloodstream than uninfected controls, and LPS levels correlate with markers of immune activation (CD38 expression on CD8 T cells). LPS is typically a product of gram negative bacteria, and LPS levels are measured in other settings involving microbial translocation such as inflammatory bowel disease. Elevated LPS alone, however, does not necessarily prove that microbial translocation is occurring, as pathogens can also be source.

The researchers also suggest that LPS levels are not elevated in acute/early HIV infection because of anti-LPS antibodies (known as EndoCAbs). When immunodeficiency worsens, they argue, these antibodies wane and levels of LPS increase. Additionally, they found reduced EndoCAb levels in people with acute/early HIV infection compared to uninfected controls and a further reduction in EndoCAb levels in chronic HIV infection versus acute/early infection. These data suggest that HIV-related immunodeficiency impairs the EndoCAb response.

The effects of antiretroviral therapy on LPS levels were also investigated. Out of 28 individuals studied, 24 showed a decline in LPS levels after 48 weeks of ART, and there was a correlation between the magnitude of the decline and CD4 T cell count increase. However there was no correlation between CD4 T cell counts and LPS levels prior to the initiation of ART.

The paper also addresses the paradox that SIV-infected sooty mangabeys experience CD4 T cell depletion of the gut but do not developed an AIDS-like illness by speculating that the monkeys may have evolved other mechanisms to prevent microbial translocation. In a commentary that accompanies the Douek article, Barton Haynes of Duke University notes unanswered questions regarding the LPS hypothesis, including the observation that immune activation is high during acute phase HIV infection—before there is evidence of LPS elevation.

Brenchley JM et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med. 2006 Dec;12(12):1365–71.

Haynes BF. Gut microbes out of control in HIV infection. Nat Med. 2006 Dec;12(12): 1351–52.

Since CROI 2006, there have been three published reviews which reflect the divergent perspectives on the importance of the GALT in HIV pathogenesis outlined in the introduction to this article. Jason Brenchley, David Price and Daniel Douek from the VRC offered "HIV Disease: Fallout from a Mucosal Catastrophe?" in *Nature Immunology*. Despite the title's question mark, this piece strongly defends the notion that the GALT is central to HIV pathogenesis in language that drifts toward excessive certainty (one section begins: "Now that we have established that it is the virus in the acute phase of the disease rather than immune activation in the chronic phase that is responsible for the bulk of CD4 T cell depletion..."). In essence, the review suggests that HIV wreaks an almost instantaneous blitzkrieg in the GALT, people lose half their memory CD4 T cells within a matter of weeks, and, to top it off, commensal bacteria leak out of the gut and cause immune activation.

Partly in response to the review by Brenchley and colleagues, Zvi Grossman, Martin Meier-Schellersheim, William Paul and Louis Picker published "Pathogenesis of HIV Infection: What the Virus Spares is as Important as What it Destroys" in *Nature Medicine* shortly afterward. They mention the mangabey data, and present their case that the virus spares, at least initially, the long-lived naïve and central memory CD4 T cells which are crucial to immune protection. They note that these long-lived CD4 T cells can regenerate the short-lived effector CD4 T cells that seem most affected by HIV initially. The authors also argue that immune activation could be sufficient to account for the gradual erosion of long-lived CD4 T cell populations. Although the precise nature of the antigens driving immune activation remain obscure (particularly the contributions of HIV-derived versus other antigens), these researchers contend that it's unlikely that commensal bacteria play a major role (again citing the mangabey GALT data). The paper is considerably more circumspect than the VRC's offering, and ultimately stresses that ignorance regarding the mechanisms governing T cell homeostasis under normal conditions is perhaps the most significant barrier to a full understanding of HIV pathogenesis.

The only researchers pondering the role of nascent HIV-specific CD4 T cell responses in all this, the Australians Anthony Kelleher and John Zaunders, were relegated to a lowlier journal called *Current HIV/AIDS Reports* where they authored "Decimated or Missing in Action: CD4+ T Cells as Targets and Effectors in the Pathogenesis of Primary HIV Infection." The review echoes the points made by Grossman and colleagues regarding the uncertain impact of early GALT CD4 T cell depletion on the long-lived memory CD4 T cell pool. However, the crux of the paper is that, somewhere amidst the many immunological and virological events that have been described during acute HIV infection, a primary HIV-specific CD4 T cell response is occurring. A primary response involves the recruitment and activation of naïve CD4 T cells specific for HIV antigens and their subsequent proliferation and development (or maturation) into HIV-specific memory CD4 T cells. While HIV-specific memory CD4 T cell can be detected within a few weeks of acute HIV infection, they typically lack the ability to perform the full spectrum of functions normally associated with memory CD4 T cells and are also more likely to be infected with HIV than CD4 T cells of other specificities. Kelleher and Zaunders argue that a better understanding of this early disruption of the first generation of HIV-specific memory CD4 T cells may provide crucial insights into both disease pathogenesis and correlates of immunological control of HIV replication.

Forging Ahead

The pursuit of science is not immune to fads and fashions, and many theories of HIV pathogenesis have briefly caught the imaginations of researchers, only to be undermined by the emergence of new data and consigned to the scientific scrapheap. Although sooty mangabeys appear to be pointing the GALT theory in the same direction, it is premature to conclude that its fate is sealed. The GALT contains a significant number of the body's T cells, and elucidating HIV's effects in this important immunological milieu will remain critically important, even if some of the initial data turns out to have been over-interpreted. The debates regarding these studies serve as a reminder that gaining an understanding of HIV pathogenesis requires grappling with the effects of the virus not just in the blood, but in the key immunological thoroughfares of the human body.

"The mechanism governing the loss of T cells continues to be debated."

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Kelleher AD, Zaunders JJ. Decimated or missing in action: CD4+ T cells as targets and effectors in the pathogenesis of primary HIV infection. Curr HIV/AIDS Rep. 2006 Feb;3(1):5–12.

Stavudine Associated with Risk for Type-2 Diabetes

Simon Collins, HIV i-Base

The use of stavudine (d4T) has dramatically fallen in most Western countries, primarily due to high risk of lipoatrophy, and additive mitochondrial-related toxicity with other reverse transcriptase inhibitors. However, globally it remains one of the most widely ARVs prescribed first line therapy (in d4T/3TC/nevirapine), as the basis for the least expensive WHO-recommended fixed dose combinations (FDCs).

Further caution against use of d4T as a long-term treatment option was highlighted in an analysis of the use of d4T and the risk of diabetes mellitus (DM) from the D:A:D Study given in an oral presentation at the biannual Glasgow HIV conference by Stephane de Wit.

D:A:D is a prospective observational study of 23,437 HIV patients that has a focus on toxicity and safety issues relating to ARV treatment, including lipodystophy, cardiovascular risk and hepatotoxicity, and where diabetes mellitus (DM) is collected as a study endpoint.

The incidence of DM in the D:A:D study is comparable to that in HIV-negative populations, and this analysis aimed to identify whether specific antiretrovirals (ARV) were associated with new onset DM.

However, the rate of DM (/1000 PY) increased from 3.96 in those unexposed to d4T to 8.20 in those exposed for 2–3 years. No other ARV was significantly associated with DM after controlling for d4T use.

Time-updated total cholesterol, HDL-cholesterol, and triglycerides were all associated with DM. Adjusting for each of these separately reduced slightly the relationship between d4T and DM. While lipodystrophy was significantly associated with DM (1.37, p=0.008), adjustment for this did not modify the relationship between d4T and DM. This led the authors to conclude that "d4T potentially directly contributes to insulin resistance, rather than through lipodystrophy."

De Wit S, Sabin CA, Weber R et al. Relationship between use of stavudine and diabetes mellitus. 8th International Congress on Drug Therapy in HIV Infection, 12–16 November 2006, Glasgow. Oral abstract PL9.5

Generic Efavirenz/Tenofovir/FTC Combo

Indian generic drug maker Cipla has launched a new fixed dose combination pill called Viraday, a combination of efavirenz 600 mg, tenofovir 300 mg and emtricitabine 200 mg (a generic equivalent of Atripla). At a retail price of 5,200 rupees a month ($117), Viraday is expected to cost about 10–15% of the U.S. price for the brand name equivalent—although it will still cost about 10-times more than a generic regimen containing nevirapine and stavudine. Gilead and Merck, the makers of Atripla, have not yet announced if their product will be made available in the developing world through Gilead's Access Program at a no-profit price.

Compulsory License for Efavirenz in Thailand

Thailand will issue a compulsory license for use by the government to improve access to efavirenz.

The price that patent holder Merck charges in Thailand (1,500 baht/month—US $41) is double that charged by Indian generic manufacturers (800 baht/month—US $22).

The compulsory license will apply both to import and local production of the drug. The Thai Government Pharmaceutical Organization (GPO), who manufacture antiretrovirals for use in Thailand, is developing its own production of efavirenz which is scheduled begin next year.

In the meantime, the compulsory license will allow Thailand to import generic efavirenz from India.

Why Do People Still Die After Taking ARVs? Is it the Brand of Drugs?

Email response to AIDS India e-forum:

I would like to bring in another angle why people face a problem or death even after on ARV treatment: It is lack of treatment literacy.

I mean to say many of the people living with HIV don't have required/sufficient knowledge about the treatment they are taking, but simply rely on the doctors who don't always have the time to explain. And we still see some doctors giving wrong prescriptions, e.g. 2 drugs instead of 3 or more.

Regarding particular brands: I am on ARVs (3TC+AZT+NVP) for the last 4 years, and I have take all the brands that are available in India: Cipla, Ranbaxy, Hetero, Aurobindo, Strides et al; whatever is the cheapest for me—it's not a problem.

I am on AZT, so I closely monitor my hemoglobin (Hb), and I'll take anything to improve Hb as I am prone to anemia. I am on NVP so I watch my liver and don't do things to hurt my LFTs.

We must scale up treatment literacy in order to have successful HIV treatment programs.

Loon Gangte
Delhi Network of Positive People

GRACE under Pressure

By Rob Camp

Tibotec's clinical development program for the protease inhibitor darunavir (Prezistia, TMC114) delivered the drug to market several months ahead of schedule. But even as it began shipping to pharmacies around the country one nagging uncertainty remained: Would darunavir be safe and effective for women? Few women had enrolled in Tibotec's series of large Phase 3 studies (POWER 1, 2, and 3) that the FDA relied upon to make its approval determination, so consequently there was little information about how well the drug suppressed HIV in women, whether women had any characteristic side effects, and whether the drug was absorbed into the bloodstream the same as in men.

Tibotec was by no means unique in gaining approval for a new drug with only limited data on women. Few drug companies are keen to enroll women in the Phase II studies that precede the large Phase III trials because the risks of toxicity are not yet well established. Women can become pregnant, and because no one wants to expose a developing fetus to unknown risk, women are not often enrolled in drug trials before Phase III. Even then there are many barriers to the full participation of women in drug research. Because Tibotec's POWER studies actually began as a Phase II trial that rolled over into a Phase III trial, it is not surprising that so few women participated in the studies.

There may be many reasons why so few women enter clinical trials. For salvage trials like TORO and POWER, it may be that there are fewer women than men with extensive drug resistance. It's also likely that women with HIV—who tend to be poor and live in large cities—have less access to the academic medical centers where so much drug research takes place. It's also likely that women are much more cautious about putting their bodies into the hands of researchers they don't necessarily trust, and that many women's experience with medical professionals has left them wary.

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Few Women Enrolled in Recent Clinical Trials

Trial (drug)	Total enrollment	Number of women enrolled	Number of women who received test drug
TORO (enfuvirtide)	995	99 (10%)	66 (6.6%)
RESIST (tipranavir)	1159	141 (12.2%)	80 (6.9%)
POWER 1,2 (darunavir)	458	53 (11.6%)	53 (11.6%)

What is GRACE?

GRACE is a non-randomized, open-label, multi-center, Phase III trial designed to evaluate efficacy, safety, and tolerability of darunavir/r in a 48-week treatment period. The study will be conducted in the U.S., Puerto Rico, Mexico and Canada, and will enroll 420 persons from 55 sites. The protocol states that 320/420 (70%) subjects enrolled will be women and each GRACE study site will be required to recruit and maintain at least 70% female enrollment. A male subject will not be allowed to enroll unless his addition will not compromise the 70% quota. There will also be race-based quotas, with a 30% cap on the number of white men able to enroll (10% overall), so meaningful comparisons can be made by race as well as sex.

What will GRACE Tell Us?

The primary objective of the trial is to evaluate sex differences in treatment response—defined as viral load <50 copies/mL—to darunavir/r plus an optimized background regimen (OBT) over a 48-week treatment period. Secondary objectives will determine the change in viral load and in CD4 count; determine the percentage of participants who discontinue due to lack of virologic response or due to an adverse event; evaluate changes in lipid profiles, metabolic parameters and any change in cardiac risk score; and evaluate safety, tolerability, and quality of life. All of these endpoints will be analyzed by sex, as well as by race.

Can I Join?

GRACE requires only that participants have experienced minimal virologic failure (or intolerance) with a prior regimen (either PI- or NNRTI-based). This is not the advanced population for which darunavir/r is currently approved. It is an earlier "second-line" group, and future approval for this indication in this population is dependent on results from GRACE.

Excluded Populations

Women who are pregnant or breast-feeding are excluded from GRACE. Dr. Thompson said, "Although no teratogenicity issues were identified in animal studies, no data have been obtained in pregnant women. The sponsor is considering a PK substudy for women who become pregnant during the trial, but that has yet to be developed."

What Now?

Details on the GRACE study can be found at www.clinicaltrials.gov. The study is currently enrolling, and should report some preliminary data within a year.

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Nevertheless, 35% of the HIV-infected population in the U.S., Canada, Europe, Brazil, and Argentina (all places where darunavir was studied), are women. In many places women make up the majority of people with HIV, yet even in the most successful cases, it is rare for the enrollment of women in an HIV drug trial to exceed 25%.

Industry-sponsored HIV drug trials designed and conducted expressly for women have been extremely rare. Recently, however, as one of its post marketing commitments to the FDA, Tibotec launched a new study called GRACE that will by design enroll a majority of women.

The FDA negotiated with Tibotec to "Conduct a study of darunavir/r in treatment-experienced female patients to elucidate any potential gender differences in efficacy and safety" post-approval. GRACE was designed to collect "comprehensive and meaningful" data on the use of darunavir in a racially diverse group of 320 women and 100 men.

Melanie Thompson, founder and principal investigator of the AIDS Research Consortium of Atlanta, is an investigator in GRACE. She thinks that if drug companies want full approval for a new drug, they had better study it in women.

"Specific data on pharmacokinetics, toxicity, and efficacy according to gender should be required by FDA for full licensing of all antiretroviral drugs. A well-managed conditional approval program would assure that studies begin in earlier phases of development for most drugs, and that women are included in higher numbers or in specific women-centered trials earlier. This should be required as part of a phase IIB package for all drugs."

Heidi Nass is a community advocate who works at the University of Wisconsin HIV Clinic and consulted with Tibotec during the design of GRACE: "This trial is poised to show that women can be enrolled and retained in clinical trials when the trials are relevant to their lives and they are given an opportunity to participate. For too long, women in research have been treated like a different species whose needs and wants are so foreign as to be impossible to address. It's about time someone challenged that in a meaningful way."

New HIV Drugs Needed for the Next Decade

By Bob Huff

The greatest unmet medical need in HIV medicine worldwide is for better treatments for people starting treatment for the first time (treatment-naïve patients). The world has made great progress in bringing antiretroviral (ARV) drugs to more than a million people in Africa and elsewhere in the developing world during the past few years. Yet, with 40 million people infected worldwide and perhaps a quarter of them in immediate need of therapy, huge gaps remains in the availability of treatment, and over 7,000 people with HIV continue to die everyday.

The most widely used ARV regimen in the developing world contains nevirapine, stavudine, and lamivudine. Although this combination is highly effective in suppressing HIV, its low cost and availability in easy-to-use combination pills from a number generic manufacturers are the key factors determining it widespread use. If it were not so affordable, this drug regimen would likely not be one's first choice. In 2004,

"HIV drug developers still have important work ahead of them."

stavudine was removed from the list of preferred first-line drugs in the U.S., and nevirapine has never appeared on that list. The standard first-line HIV regimen in the developing world urgently needs a second look.

Stavudine (d4T), although highly effective as an anti-HIV drug, has been associated with body fat changes known as lipoatrophy, and may have been one of the chief culprits in the epidemic of facial fat wasting that affected so many people on ARVs during the first decade of HAART. After only a few years of widespread use in the developing world, reports are starting to appear of body fat abnormalities in patients in Lesotho, Thailand, and elsewhere. The appearance of such highly visible side effects in people taking ARVs has the potential to damage a sometimes fragile public perception of HIV treatment. It would be tragic if ARVs came to be shunned in some communities because they were seen as the source of disfiguring and stigmatizing side effects. Another serious side effect of stavudine use in some patients is painful peripheral neuropathy, which can cause a burning sensation in the toes and fingers. Zidovudine (AZT), a more expensive cousin of stavudine, is an alternate drug choice, although it too has been associated with the development of fat wasting problems, albeit at a slower pace. Zidovudine also can contribute to anemia, a serious problem for pregnant women and many others in the developing world with suboptimal nutrition.

Tenofovir is now the most commonly used replacement for stavudine and zidovudine in the rich countries because it is highly effective and causes no serious side effects in the great majority of people using it. Although tenofovir does not have tolerability problems, it has been associated with a reduction in kidney function and possibly with diminished bone mass, side effects that are mild and stable in most people but give doctors a bit of worry and require monitoring, especially in patients with prior kidney problems. Unfortunately, careful monitoring is a luxury that can not be depended upon in resource-poor settings, although clinical trials of tenofovir in Africa have not uncovered any serious problems when using the drug in routine practice under limited conditions. One formidable problem, however, is that tenofovir is many times more expensive than stavudine, and although future competition between generic manufacturers may lower the cost, tenofovir will likely never be as cheap as the current standard. For the foreseeable future, the developing world is stuck with stavudine.

The Non-nukes

In the North, initial non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens are most commonly anchored with efavirenz and backed up by tenofovir and emtricitabine (a drug very similar to lamivudine). These three drugs are also now available in a convenient, once-daily, single tablet from their brand name makers.

As anchor drugs of an NNRTI-based regimen, both nevirapine and efavirenz share many similarities. They both effectively control HIV and both remain in the bloodstream for extended periods. But both are also susceptible to loss of activity if HIV develops only one or two resistance mutations, and developing resistance to one drug results in resistance to the other. In the rich countries, efavirenz is more commonly prescribed because it is considered more potent and because nevirapine requires much closer monitoring when initiating the drug in first-time patients due to severe and occasionally fatal liver problems that have developed in a few people. Nevirapine should not be initiated in women with CD4 counts higher than 250 cells/mm^3 or in men with CD4 counts higher than 400 cells/mm^3. Nevirapine is also a difficult drug to use in combination with certain drugs used to treat tuberculosis, one of the most deadly coinfections in the developing world.

But even the best available choices for privileged patients in the North leave much to be desired. Efavirenz is a convenient and highly effective drug and most patients probably find it trouble-free over the long-term. But efavirenz causes profound sleep disturbances and exhaustingly vivid dreams for many people who may tolerate these side effects for a year or so, but are relieved when finally switched to something else. And because efavirenz has been associated with birth defects, it should not be used in women who are or want to become pregnant. For them, nevirapine or a protease inhibitor is a safer choice.

In the developing world, the best price for an efavirenz-based combo is five-times that of a generic nevirapine regimen, which, for a national treatment program, means that fewer people can be treated and the population-wide impact diminished. Basing a regimen on a protease inhibitor adds additional costs. For mass treatment programs conducted with limited public health resources in very poor countries, pennies per day matter, and the best price for the best available regimen is often out of reach.

After the First Drugs are Gone

Because resistance to nevirapine is relatively easy to produce, and because nevirapine resistance also eliminates efavirenz as an option, there is already a growing need for second-line therapies based on the protease inhibitors for treatment programs in the developing world. This need has not received a lot of attention, partly because of the urgency of getting first-line therapies rolled out to those who desperately need them, and partly because the tools for monitoring first-line treatment failure are not widely available outside of a few well-resourced ARV treatment programs like the U.S. Government's PEPFAR. But when the need for switching patients to protease inhibitors is confronted it immediately becomes apparent that the cost of treatment rises dramatically. The cheapest, most practical, and most widely available protease inhibitor in the developing world, Abbott's Kaletra, is four to five times more expensive than nevirapine, even when obtained through the company's no-profit pricing program for the developing world.

"The standard first-line regimen in the developing world urgently needs a second look."

While there is an unmet medical need for safer, cheaper, more potent, more durable, and more tolerable HIV drugs for all of the world's HIV patients, it is the crushing burden of HIV in the developing world that now underscores the urgency of finding better ARV drugs.

Characteristics of an Ideal Regimen

Obviously an ideal new drug for treating HIV in the developing world must potently suppress HIV replication. But it should also work against a broad range of HIV subtypes and against virus that has lost susceptibility to other drugs. Ideally, a new drug would target a unique point in the viral lifecycle so critical to HIV's survival that resistance mutations would be rare, or, if they occurred, would produce a drastically impaired virus. A ideal drug should remain in the bloodstream long enough to allow once-daily dosing—and be relatively forgiving of the occasional

missed dose. Optimally, the drug would be so potent that it could be used on its own, without NRTI support. Alternatively, it would be easy to formulate together with other HIV drugs into a single pill without any special technology.

It should also enter and pass through the body without affecting the blood levels of other drugs or being much affected by them in turn. Not only should the long term safety profile of this ideal drug be benign, but it should have few of the tolerability discomforts like mild nausea or diarrhea that accompany so many other drugs. Doctors need to feel confident that they can start a patient on this drug and not have to follow up for several months or more. The need for monitoring should be minimal. Patients need to know that the drug can reliably roll back their HIV disease without making life miserable or increasing their risk for experiencing other medical problems.

"Even the best available choices for priviledged patients in the North leave much to be desired."

Finally, an ideal new ARV for the developing world must be cheap and easy to manufacture, and the patent holder must be willing to allow multiple generic manufacturers to make abundant quantities available wherever they are needed. A wonderful drug like this would be in demand in the rich countries too, and that's where the innovating company would expect to make its investment pay off.

Coming in 2007

This set of specifications is a tall order, but there are encouraging signs that better drugs are in the pipeline. Merck is racing forward with development of a new drug that works by inhibiting a unique target in the HIV lifecycle called integrase. So far, Merck's integrase inhibitor appears to be quite potent and has not revealed any particular safety problems (day-to-day tolerability remains to be seen, with some trial participants complaining of increased flatulence). A minor drawback for Merck's first offering in this new drug class is a requirement for twice-daily dosing. The biggest medical unknown yet to be answered by the clinical trials in progress is whether or when resistance mutations will arise that defeat the drug. The biggest commercial unknown is how much it will cost to manufacture the integrase inhibitor, how much Merck will charge in the developing world, and what will be the company's policy on allowing third-party generic drug makers to produce the drug for low-profit markets. Merck's integrase inhibitor may receive U.S. approval by late 2007.

Another new drug due in 2007 that also blocks HIV infection in a unique way is Pfizer's entry inhibitor, maraviroc, a CCR5 antagonist that prevents the virus from entering target CD4 immune cells. Although data is still sparse, in preliminary studies, the drug was effective, and no safety or tolerability issues have emerged so far. One limitation is that maraviroc is only effective at blocking HIV that uses the CCR5 coreceptor to infect new cells. HIV variants that use a different coreceptor are not inhibited by the drug, and these variants may be present in 10% to 60% of people with HIV, mainly depending on how long they have been infected. This means that maraviroc may not be reliable for use in broad populations without specialized and expensive diagnostic tests.

New NNRTIs are also being developed by Tibotec that address problems with nevirapine and efavirenz, and TMC125, also due in 2007, may be useful in communities where primary, transmitted nevirapine resistance is a problem.

There is an unmet medical need for better HIV drugs for initial and subsequent therapy for all kinds of patients, in all parts of the world. A drug with ideal qualities for the developing world would also be what is needed in the North by treatment-naïve patients and by highly treatment-experienced patients who have developed resistance to nearly all of the 20-plus HIV drugs available to them. New drugs on the visible horizon may meet some of these criteria but the ideal is still out of reach. Barring the surprise discovery of an effective vaccine or some other unexpected breakthrough, HIV drug researchers still have a lot of important work ahead of them.

A version of this article first appeared in GMHC Treatment Issues.

Early Access to Coming Drugs

Expanded access programs have opened to offer early access to three experimental drugs expected to be approved during 2007.

Contact your doctor or call for more information

TMC 125, an NNRTI from Tibotec Pharmaceuticals
866-889-2074

MK0518, an integrase inhibitor from Merck
877-EARMRK1

Maraviroc, a CCR5 antagonist from Pfizer
888-275-4478

Optimizing Antiretroviral Therapy for HCV Coinfected People

By Tracy Swan

Antiretroviral therapy (ART) may delay liver disease progression in people coinfected with viral hepatitis by preserving immune function. Conversely, viral hepatitis coinfection complicates HIV treatment, because it increases the risk for treatment-associated hepatotoxicity (liver injury) and discontinuation of antiretroviral therapy.

Despite concerns about hepatotoxicity, the benefits of antiretroviral therapy outweigh the risks for coinfected people. In fact, ART may be a life-saving intervention for some coinfected people, since serious HCV-related liver damage is most likely to occur in people with less than 200 CD4 cells. Since the majority of coinfected people do not experience serious antiretroviral-induced hepatotoxicity, clearly HIV treatment should not be withheld from people coinfected with viral hepatitis, although careful monitoring for signs and symptoms of hepatotoxicity is warranted.

Better Research, Better Tools Needed

Given the prevalence of viral hepatitis coinfection among people with HIV, there is an urgent need for much more information about drug levels, long-term safety and tolerability of antiretroviral agents in this population. FDA should go beyond recommending pharmacokinetic (PK) studies of antiretroviral agents in persons with hepatic impairment by requiring PK studies in coinfected persons with moderate-to-serious liver damage prior to approval. When indicated, sponsors should support PK studies of approved antiretroviral agents.

Longer-term data are needed, since drug levels may accumulate over time or liver damage may progress, thus changing the safety, tolerability and efficacy profiles of antiretroviral agents. Coinfected people in Phase II through Phase IV studies should be carefully monitored if we are to better characterize the safety, efficacy and tolerability of antiretroviral agents.

New tools are also needed to simplify assessment of liver damage, and make PK results clinically relevant to persons who have not had biopsies. Public and private sector research partnerships should support development and validation of non-invasive serum biomarker panels. Designers and sponsors of long-term cohort studies need to incorporate serum biomarker panels as part of long-term follow-up of coinfected participants.

Activists and regulators should continue their collaboration to beef up pre- and post-approval requirements. Drug labeling should reflect lack of specific data in coinfected persons due to incomplete pre- and/or post-marketing commitments.

More HCV recommendations at:
www.treatmentactiongroup.org

What is Hepatotoxicity?

Some medications can cause liver injury, ranging from mild to life threatening. Drug-induced liver injury may be asymptomatic, but it usually can be identified by laboratory tests. Injury to liver cells is indicated by abnormally high levels of two liver enzymes, alanine aminotransferase (ALT) and aspartate amino transferase (AST). Some drugs cause bile duct blockage, referred to as cholestatic injury, which is indicated by elevated gamma-glutamyl transferase and alkaline phosphatase levels. Although cholestatic injury usually resolves after discontinuing medication, in rare cases, liver failure may occur.

Antiretroviral-induced hepatotoxicity is characterized by elevated liver enzyme levels with or without the following additional symptoms of liver inflammation: jaundice, fatigue, loss of appetite, abdominal pain, nausea, vomiting, diarrhea, light-colored stools, and dark urine. In addition to these symptoms, rash may precede or accompany nevirapine-induced hepatotoxicity syndrome.

"Some medications can cause liver injury, ranging from mild to life threatening."

Hepatotoxicity often occurs within weeks of starting a new antiretroviral regimen or agent, but may also develop with continued drug exposure over a longer period of time. In many cases, providers can closely monitor and "treat through" hepatotoxicity. However, experts recommend that all medications be discontinued when liver enzyme levels reach ten times the upper limit of normal within the first four weeks starting of a new ART regimen. Continued use of a hepatotoxic drug or regimen may be life threatening.

Several drugs from the three major classes of antiretroviral agents, NRTIs, NNRTIs, and PIs, have been associated with hepatotoxicity, and, in 2005, severe liver toxicity was responsible for Glaxo SmithKline stopping all clinical trials of its experimental CCR5 antagonist aplaviroc.

Mechanism of Hepatotoxicity

While coinfection with viral hepatitis significantly increases risk for antiretroviral-associated hepatotoxicity, several additional factors can also cause or contribute to liver toxicity. These can include alcohol use, direct toxicity of a specific drug, and interactions between ARV agents and medications used to treat a range of HIV-related comorbidities, namely opportunistic infections and psychiatric conditions. Genetic differences in

drug metabolizing enzymes and related host factors may also affect an individual's risk for hepatotoxicity.

In coinfected people, ART-related immune restoration may result in flares of symptomatic hepatitis, and certain antiretroviral agents may exacerbate hepatic steatosis (the accumulation of fat in the liver), a condition associated with more serious liver damage in persons with hepatitis C.

The liver is involved in the metabolism of several antiretroviral agents, and serious liver damage may alter the liver's metabolic or excretory capacity. Yet the extent of liver damage can vary widely among coinfected individuals, ranging from mild fibrosis to serious liver scarring, known as cirrhosis. Coinfected people with more serious liver damage (defined as Metavir biopsy score of F3 or F4) are more likely to develop antiretroviral-associated hepatotoxicity than those with lower Metavir scores (F1 or F2) and less liver damage[1].

For vulnerable persons with more advanced liver disease, metabolic alterations may lead to increased or decreased drug exposure, resulting in either the accumulation of toxic drug levels—with accompanying increased risk for side effects and toxicity—or a decline to subtherapeutic levels and an increased risk for developing drug resistance. Metabolic alterations may also increase the potential for drug-drug interactions.

"Metabolic alterations may lead to increased or decreased drug exposure."

Antretroviral Drug Levels and Hepatotoxicity

Antiretroviral drug levels must be high enough for a drug to achieve its effect without causing toxicity; the range between a minimally effective dose and a toxic dose is known as the therapeutic window. Doses above the therapeutic window may aggravate side effects and increase toxicity, leading to discontinuation, or worse. It is reasonable to assume that some cases of hepatotoxicity result from chronic dosing above the therapeutic window. Furthermore, the different therapeutic window may vary in each individual depending on coadministered prescription drugs and genetic, immunologic, or environmental factors.

Pharmacokinetic (PK) studies assess what happens to a drug in the body: how it is absorbed, distributed, metabolized and eliminated. Pharmacodynamic (PD) studies evaluate drug activity, or what a drug does to the body. Data from both types of studies are needed to characterize the hepatic safety and proper dosing of antiretroviral agents in coinfected people. It is important that coinfected people are included and closely observed in Phase II and Phase III studies of new drugs so that longer-term data on hepatic safety and tolerability of antiretroviral agents may be collected.

Some data on drug levels in people with serious liver damage are available. In 2003, FDA issued guidance to industry for conducting pharmacokinetic (PK) studies in persons with hepatic impairment (defined as mild-to-moderate cirrhosis according to the Child-Pugh scoring system). FDA recommends, rather than requires, these studies when hepatic metabolism and/or excretion accounts for a substantial portion (>20 percent) of the absorbed drug or elimination of a parent drug or active metabolite. In addition, even when the drug or active metabolite is eliminated to a lesser extent than 20%, FDA strongly recommends that industry conduct these studies whenever labeling, literature, or available information suggests that the drug has a narrow therapeutic range.[2]

Although hepatic impairment studies performed to date have yielded useful information, their results do not apply to all coinfected people—only those who have developed cirrhosis. Antiretroviral drug levels are not studied in coinfected people with mild to moderate liver damage, and not all approved antiretroviral agents have been studied in cirrhotics.

Prior to approval, FDA should require that PK studies of antiretroviral agents are conducted in coinfected people with varying degrees of liver damage, particularly those with more advanced liver damage such as bridging fibrosis and cirrhosis. Ideally, barring any significant concerns about drug safety, PK studies in coinfected persons should be underway before Phase III trials and Expanded Access Programs are launched.

PK studies are only the first step towards optimizing antiretroviral therapy for coinfected persons. Additional data are needed, particularly longer-term assessment of antiretroviral drug levels, side effects, safety, efficacy, tolerability and liver disease progression in coinfected persons.

Biopsy Alternative Needed

However the major challenge in designing such studies is the lack of a non-invasive and inexpensive method to assess liver damage in research and clinical practice. Liver biopsy is the best way to determine what is happening to liver tissue, but it is expensive, invasive, can be painful, and carries a small risk of complications; rarely, these have been life-threatening. Ongoing research is evaluating several alternatives to liver biopsy, but none have replaced the gold standard.

One potential solution involves using a combination of blood tests, known as serum biomarker panels, to assess the extent of liver damage in clinical practice. Although many experts do not believe that serum biomarker panels are a viable substitute for liver biopsy, these panels are likely be used in the clinic. One way to understand the value of these panels would be to recruit coinfected people who had been biopsied into PK studies, then compare results from serum biomarker testing to biopsy. If a good correlation between biopsy and serum biomarker panel results were found, this would mean that valuable and clinically relevant data could be collected.

Drug Levels Matter

More research on ARV drug levels in coinfected persons is also warranted, particularly since conflicting data have emerged from many scattered, small PK studies of single drugs. For example, Dominguez and colleagues reported that coinfected participants had significantly lower levels of lopinavir/r vs. those with HIV alone in Hepadose, a recent PK study measuring PI and NNRTI levels in 132 HIV-positive people, 70 of whom were coinfected. Hepadose measured trough PI and NNRTI plasma concentrations in 132 people (the trough is the lowest level of a drug present in the bloodstream immediately prior to the next dose). But a different study from Dickinson and colleagues did not find significant differences in plasma levels of lopinavir/r according to HCV status, or even among cirrhotics[3,4].

Hepadose also detected significantly higher trough concentrations of efavirenz, nevirapine and nelfinavir in coinfected people compared to people with HIV alone. In particular, the study saw trough concentrations of efavirenz and nevirapine that were significantly above therapeutic range in 56% of coinfected patients with fibrosis scores of F0 to F3, and a whopping 86% of those with F4 (vs. 24% for those with HIV alone).[3]

Other studies have reported similar findings. Jeantils and colleagues detected above-the-range trough concentrations of efavirenz in six of twelve coinfected individuals. Accordingly, the investigators successfully reduced daily efavirenz doses from 600mg to 400 mg[5].

Until more data are available on ARV drug levels in coinfection, therapeutic drug monitoring (TDM) may be useful for coinfected individuals, particularly those with advanced liver damage, and persons experiencing elevated liver enzyme levels, side effects, or virologic failure. TDM studies provide individualized plasma levels of protease and/or non-nucleoside reverse transcriptase inhibitors (nucleoside analogue drugs, which become active only inside of cells, require intracellular assays to measure drug concentrations). Dosing is adjusted accordingly, as needed. Unfortunately, TDM is an individualized measurement, and not applicable to anyone other than the person being studied. TDM is more commonly used in Europe than the United States, where it is costly and difficult to obtain outside of a clinical trial.

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What's Next?

Leadership Lacking in Move From 3x5 to Universal Access

By Mark Harrington

The past year saw a number of *post mortems* about the World Health Organization's "3x5" initiative to support countries in treating at least 50% of their HIV-infected populations in need of antiretroviral therapy. These commentaries ranged from almost gleeful *schadenfreude*, to a detailed yet in parts scathing evaluation commissioned by the Canadian government, to a series of activist-written country reports. The year 2006 also saw the untimely death of WHO Director General JW Lee, who staked his reputation on the 3x5 initiative, the advent of Kevin De Cock as new director of WHO's HIV Department, and a tepid commitment by global and national leaders to move beyond "3x5" to achieve universal access to antiretroviral therapy (ART) for all who need it.

One particularly low point occurred at the UN's General Assembly Special Session on AIDS (UNGASS) in June, when the African delegation, led by Egypt, Gabon, and South Africa—the last of which had been a dedicated foe of "3x5" since its inception--refused to lobby for global treatment targets in the UNGASS declaration.

However a turning point for South Africa may have been achieved in August 2006, when before a worldwide audience at the International AIDS Conference in Toronto, Mark Heywood of the AIDS Law Project called for the resignation of South African minister of health Manto Tshabalala-Msimang, who had spent the past five years stoutly defending the irrational HIV policies of South African President Thabo Mbeki. At the same time, in Cape Town, hundreds of activists from the Treatment Action Campaign (TAC) demonstrated for the rights of HIV-positive South African prisoners to access antiretroviral therapy.

Whether by coincidence or not, in mid-September the South African health minister was hospitalized in Johannesburg for a lung infection. In her absence South Africa's deputy health minister Nozizwe Madlala-Routledge stated that government has been in "denial at the very highest level" over AIDS, commissioned a revised national plan to triple the number of people receiving ART and to halve the new HIV infection rate, and challenged the President to take an HIV test.

It is too soon to tell how durable and concrete the results of the apparent rapprochement between TAC and the South African government will be. But no one can doubt that the government's turnaround owes an incalculable amount to the unrelenting activism of TAC over the past eight years, and this in turn demonstrates that strong activist movements can transform AIDS policy in countries with functioning democratic institutions. Whether the achievements of TAC can be duplicated in countries which lack full rights for civil society organizations remains to be seen.

In many ways the most difficult part of the worldwide effort to scale up antiretroviral therapy is just beginning. Some countries such as Botswana, Brazil, Malawi, Thailand, Uganda, and Zambia have made substantial progress on treating a significant proportion of their HIV infected populations. Many others are midway through scale-up efforts whose ultimate success remains unclear. Some countries with very large epidemics such as India, Nigeria, and Russia are doing poorly.

Even in countries making substantial progress towards more complete ART coverage the difficulties of keeping people already on treatment healthy and starting thousands more on therapy are daunting. Many people will begin to experience drug related toxicity as they enter the second or third year on ART. Most countries lack access to safer drugs such as tenofovir. Some five to ten percent of people on ART will need a new regimen due to antiretroviral treatment failure in the coming year, yet the treatment of choice—a ritonavir-boosted protease inhibitor such as lopinavir/r (Kaletra)—remains prohibitively expensive. ART programs for HIV infected children are rare.

What is needed? More intelligent activism at all levels, such as that illustrated so dramatically by TAC in 2006, is a prerequisite. Activists need to focus their efforts on pressuring national governments to set and to meet national treatment targets, and to monitor their progress, as demonstrated by the International Treatment Preparedness Coalition (ITPC) in its scathing series of reports entitled *Missing the Target.* Activists need to ensure that countries can access high-quality generic first- and second-line antiretroviral treatment for both adults and children. They need to pay more attention to the intersecting epidemics of HIV, tuberculosis (TB), and hepatitis B and C.

Activists need to focus on the needs of people with AIDS who need treatment now—both abroad and at home. Currently in South Carolina 350 people with HIV are on a waiting list for ART coverage from the state AIDS Drug Assistance Program. This shameful situation makes explicit the lack of anything like a national plan for AIDS prevention and treatment in the United States. It's time for activists to link up their global and national work and to make alliances with others who should be part of the struggle for universal access to high quality health care for all. Twenty years after the foundation of ACT UP, the AIDS Coalition to Unleash Power, the need for accelerated, intensified, and more intelligent and targeted coalition-based activism is as clear as ever.