The 2007 Pipeline Report

Experimental Treatments and Preventive Therapies for HIV, Hepatitis C, and Tuberculosis

Treatment Action Group
New York, New York

July 2007

The 2007 Pipeline Report

Experimental Treatments and Preventive Therapies for HIV, Hepatitis C, and Tuberculosis

Treatment Action Group
New York, New York

July 2007

Acknowledgments

Written by Mark Harrington, Bob Huff, and Richard Jefferys. Reviewed by Tracy Swan, Javid Syed, Claire Wingfield, and Jen Curry. Copy-edited and proofread by Kelly Safreed-Harmon. Design and layout by Adam Zachary Fredericks.

About Treatment Action Group

Treatment Action Group (TAG) 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 life saving 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 policymakers to end AIDS.

For more information, contact:

Treatment Action Group
611 Broadway, Suite 308
New York, NY 10012

212.253.7922 - tel
212.253.7923 - fax
www.treatmentactiongroup.org
tagnyc@verizon.net

The 2007 Pipeline Report

ISBN 978-0-9791073-2-0

Table of Contents

Introduction

The *Pipeline Report* is the Treatment Action Group's annual review of experimental technologies that have the potential to solve critical unmet medical needs surrounding HIV infection and AIDS.

Pipeline reviews—a staple of the AIDS research and treatment literature—arose in the 1980s. In that era, before effective HIV treatments existed, desperate people sought every scrap of hope about all kinds of potential therapies, whether developed within the scientific paradigm or by the lights of alternative wisdom.

Pipeline reports concisely assess how soon some critical technologies might arrive to relieve our most urgent medical needs. In 1989, the clinical pipeline for AIDS treatments trickled with a few drugs that ultimately fell short of miraculous. Basic research charged ahead nonetheless, and by 1993 experimental drugs with startlingly new mechanisms of action had appeared in the pipeline. Not until 1996 did these discoveries finally converge with accurate tools for measuring viral load and with new ideas about using combination therapy to combat drug resistance, resulting in the breakthrough known as HAART.

In 2007, with over 20 approved HIV medications, we no longer feel the same urgency about every single new candidate at every stage in the development process, and this year's *Pipeline Report* limits itself mainly to drugs that have a reasonable chance of becoming approved products within the next several years. Earlier phase I studies are often exploratory outings that go no further, and some large companies prefer to keep quiet about initial clinical research until there is confidence about the putative drug's safety and activity. Staying abreast of advances in basic science and new theoretical approaches to treatment is important, but progress in solving the many pressing problems that face people living with HIV and its complications is what really matters. Ultimately, the pipeline exists to produce solutions.

For example, tuberculosis (TB) is the worst killer of people with HIV worldwide, and the greatest impediment to curing TB is the lack of a simple, reliable test to identify who actually has the disease and

requires treatment. Therefore, we desperately need to see new TB diagnostics in the pipeline. The next priority is more traditional: better drugs to treat and cure people with multidrug-resistant TB. Although research activity in both of these arenas is heating up, investment remains miniscule compared to the scope of the problem.

Millions of cases of hepatitis C virus (HCV) infection go untreated, and liver damage caused by HCV can greatly complicate HIV therapy. Research is burgeoning as small and large companies alike scramble to bring a breakthrough HCV therapy to market. But breakthroughs don't come easily, and it is difficult to predict which new agents will prove valuable. One obstacle: significant uncertainty remains about the best way to scientifically demonstrate that certain new HCV drugs are doing what we think or hope they are.

Basic science research on the most critical unsolved mysteries regarding the immune pathogenesis of AIDS may finally be yielding new ideas about the role of immune activation in the progressive loss of CD4 cells. If not certain knowledge, at least some new theories are emerging as the field of AIDS immunology enjoys a rare period of thaw and fertility.

The pipelines for prevention technologies remain unproductive. Two of the first few simple microbicide candidates have foundered in late-stage studies, while more sophisticated products are still snagged on technical problems. Meanwhile, hope springs eternal on the glacial plains of vaccine development. Although many core questions that hold this field back remain unanswered, the coming year may bring significant news, if not real progress.

The quest for better drugs to treat HIV infection will likely produce the biggest impact during the next 12 months. The anticipated arrival of three important new antiretroviral drugs is generating excitement about a potential shift in how HIV will be treated in the future. It is too soon to say if such talk is justified, but 2008 may be a year in which many people who have long struggled with multidrug-resistant HIV finally see their viral loads brought under control.

HIV Antiretroviral Drug Pipeline 2007

HIV Drugs in Clinical Trials*

Phase II	Phase III
Maraviroc (Celsentri): CCR5 antagonist—*Pfizer*	
Raltegravir (Isentress, MK-0518): HIV integrase inhibitor—*Merck*	
Etravirine (TMC-125): NNRTI—*Tibotec*	
Rilpivirine (TMC-278): NNRTI—*Tibotec*	
Elvitegravir (GS-9137): HIV integrase inhibitor—*Gilead*	
Vicriviroc: CCR5 antagonist—*Schering*	
Bevirimat (PA-457): Maturation inhibitor—*Panacos*	
TNX-355: Anti-CD4 monoclonal antibody—*Genentech (Tanox)*	
BILR 355 BS: NNRTI—*Boehringer-Ingelheim*	
Racivir: NRTI—*Pharmasset*	
Dexelvucitabine (Reverset): NRTI—*Pharmasset*	
Amdoxovir: NRTI—*RFS Pharma*	
Apricitabine (AVX754): NRTI—*Avexa*	
Elvucitabine: NRTI—*Achillion Pharmaceuticals*	

DISCONTINUED: Brecanavir (VX-385): Protease inhibitor—GlaxoSmithKline.

* This and subsequent tables only display compounds in phases II and beyond; compounds in phase I are described, where relevant, in the text.

Coming Soon to Your Pharmacy

The buzz phrase of the moment for antiretroviral therapy is "paradigm shift," which suggests the prospect of dramatic changes in how well and easily people are treated for HIV infection. Merck's first-in-class integrase inhibitor, raltegravir, is generating most of the buzz. Raltegravir wowed the 2006 International AIDS Conference by showing it could knock down HIV viral loads at least twice as rapidly as efavirenz in a treatment-naïve study population. Yet by the end of the

trial, both treatment arms had similar proportions of subjects who achieved undetectable virus, begging the question: If you wind up with durably suppressed HIV, does it matter how fast you got there?

Treatment for the Treatment Naïve

To some, "paradigm shift" means treating HIV earlier—before the CD4 cell count has dropped to a level that increases the risk of complications, and well before it has reached 200, the CD4 level at which guidelines say therapy absolutely should be started. While no clinical trial evidence tells us that starting at one point or another is better (as long as one starts above the 200 CD4 mark), the emerging belief holds that an unchecked HIV infection is never benign. The potential impact of HIV on immune capacity, the brain, and the cardiovascular system may argue for intervention, even in asymptomatic people who are at low risk for life-threatening opportunistic infections. Therefore, if trouble-free drug regimens with no toxic complications become available, it might be reasonable to use them to control HIV replication, regardless of the CD4 count.

Rilpivirine (TMC278) from Tibotec is a nonnucleoside reverse transcriptase inhibitor (NNRTI) targeting the need for gentler drugs. Although it reduced viral load a little more slowly than efavirenz (and much more slowly than raltegravir), rilpivirine is free of the central nervous system side effects that eventually cause some people to stop taking efavirenz, even when it is working well. At a compact dose of 75mg per day, rilpivirine should make an excellent candidate for inclusion in a convenient one-pill, once-a-day regimen formulation. Approval is not expected before 2009.

Merck's **raltegravir (Isentress, MK-0518)** and another first-in-class drug, the entry inhibitor **maraviroc (Celsentri)** from Pfizer, initially were developed for patients with multidrug-resistant HIV. However, they also hold a great deal of promise for treatment-naïve patients, at least in the wealthy nations. For first-line therapy, raltegravir has the minor drawback of requiring twice-daily dosing, and maraviroc requires patients to take an expensive, imperfect test to determine their likelihood of benefiting from the drug.

As exciting as these new treatments are, they will not immediately knock aside the stalwarts of first-line therapy: lopinavir (Kaletra), atazanavir (Reyataz), efavirenz (Sustiva/Stocrin), and nevirapine (Viramune). Early adopters of new HIV drugs have been burned in the past, and many doctors are likely to feel safer prescribing time-tested regimens to previously untreated patients. Furthermore, one or two new drugs won't revolutionize the treatment paradigm unless they can attain efficacy without support from nucleoside reverse transcriptase inhibitors (NRTIs), which are still generally paired in combination with a third drug in most triple-combination regimens. Ditching the NRTIs without more data could be risky if the NRTIs effectively reach the brain or tissue compartments that other drugs miss. The practice of what and when to prescribe to treatment-naïve patients may evolve with the coming generation of drugs, but the underlying paradigm of long-term if not life-long viral suppression with highly effective combination therapy is likely to endure for some time.

Treatment for the Treatment Experienced

Although the impact for previously untreated people might initially be modest, the new roster of drugs may well herald a revolution for highly treatment-experienced people who have developed resistance to most available HIV drugs. This group of so-called "salvage patients" also includes a smaller number of previously untreated people who were initially infected with multidrug-resistant HIV.

Thousands of people live with unsuppressed HIV infection because they cannot benefit from or cannot tolerate enough of the currently approved drugs to construct an effective combination antiretroviral regimen. During the ten years following the first flowering of HAART in 1996, whenever researchers developed a new drug that could help highly treatment-experienced people, there often were no other new drugs to add along with it, and treatment success was short lived. Eventually, HIV physicians and patients learned that simply adding one new drug to a failing regimen composed of previously prescribed drugs virtually was the same as using the new drug alone, with an outcome of treatment failure due to resistance.

What is exciting about this year and the next is that these toughest-to-treat patients will—if their doctors are smart about it—be able to combine several new drugs that have the power to knock down viral replication and keep it down for years to come. At least that is the hope, and it represents a convergence of circumstances that could have a huge impact on a longstanding problem.

In 2006, darunavir (TMC114, Prezista), a new protease inhibitor (PI) with a unique resistance profile, appeared on the market. Despite the drug's ability to suppress virus resistant to other PIs, relatively few patients have switched to darunavir, possibly because they have been prudently waiting for other effective new drugs to partner with it. Those drugs may finally be here.

Three new agents for salvage therapy, etravirine, raltegravir, and maraviroc, will likely come to market in the near future. Expanded access protocols have provided an early look at how these new options may be used for people with multidrug-resistant HIV.

Etravirine (TMC125), an NNRTI from J&J/Tibotec, seems to be effective against some (but not all) HIV that is resistant to efavirenz and nevirapine. **Raltegravir**, the integrase inhibitor from Merck, should also be active against multidrug-resistant HIV by virtue of its first-in-class status. Its performance in studies with highly treatment-experienced patients has been impressive.

Because these two drugs do not interfere with one another in the bloodstream, the sponsors allowed their combined use in the expanded access protocols aimed at treatment-experienced patients. The response to the opportunity to add at least two new active drugs has been dramatic. Whereas interest in the 2006 darunavir expanded access protocol was modest at best, enrollment in the 2007 etravirine and raltegravir programs has been brisk. It is not yet clear if most expanded access patients are combining these two drugs or are incorporating darunavir or enfuvirtide (T20) as a second, third, or fourth drug in their combination. Regardless, even normally dour researchers have been uncharacteristically enthusiastic as reports trickle in about long-time salvage patients achieving undetectable viral loads for the first time ever. If their viral loads remain undetectable, then the talk may be justified.

The third new drug on the scene is the CCR5 antagonist, **maraviroc (Celsentri)**, from Pfizer. This first-in-class drug is also capable of benefiting patients with long, troubled treatment histories, although a few limitations have held back enrollment in its expanded access protocol. The first problem is that blocking the CCR5 co-receptor molecules that HIV uses to infect new target T cells does not help every person who has HIV. Some forms of HIV use a different co-receptor, and the likelihood of having a virus that exclusively uses CCR5 decreases the longer one is infected. Thus, perhaps only 50% of people with more advanced disease can benefit from maraviroc.

For those with CCR5-tropic virus, maraviroc's antiviral efficacy has been impressive. Before someone starts taking the drug, though, it is highly advisable to undergo a viral tropism test to determine which kind of HIV the person has and to predict its susceptibility to CCR5 blocking. The test is expensive and results can take up to two months to obtain. Another possible deterrent is concern about the safety of a drug that blocks one of the body's own immune messenger proteins. (All previous HIV drugs have targeted viral proteins.) These issues—and the enthusiasm with which raltegravir has been received—suggest that maraviroc may not be as quickly accepted as a major player in the new salvage therapy paradigm.

Trailing Behind the Leaders

Not since the *annus mirabilis* of HIV therapy in 1996 have so many potent new drugs neared the market at almost the same time. The drugs discussed above have been in large clinical trials to study how well they are likely to work in the real world at their approved doses. In this section, we discuss a group of HIV drugs at earlier stages in development. They currently are being tested to determine optimal dosages.

Elvitegravir (GS-9137) from Gilead aims to become the second-in-class member of the integrase inhibitor family after raltegravir. A dose has been selected and the drug is slated to begin large phase III trials later this year. Elvitegravir's most apparent advantage over raltegravir is once-daily dosing, although this comes hand-in-hand with the drug's biggest drawback: dependence on pharmacokinetic boosting with ritonavir. This may be less

of a barrier for treatment-experienced patients who are likely taking a ritonavir-boosted protease inhibitor (PI). Elvitegravir may one day be used for first- or second-line treatment too, perhaps as part of a two-drug, ritonavir-boosted PI/integrase combo.

The second-in-class drug in the CCR5 antagonist family is the entry inhibitor **vicriviroc** from Schering. This drug, despite being developed by a major league company, has had a blighted history. A study in treatment-naïve patients was stopped early due to more frequent virologic failure in people taking vicriviroc compared to those taking efavirenz. The presence of another HIV drug such as ritonavir or efavirenz can significantly alter blood levels of vicriviroc, which complicates dosing. In early 2006, five cases of cancer were reported in the vicriviroc arm of a small study in patients with very advanced HIV disease. Although the cancers were not attributed to the drug, the episode raised concerns about vicriviroc and the CCR5 antagonists in general.

The complex process of bringing an HIV drug to market is fraught with so many pitfalls that it increasingly looks like only the biggest companies, those with the deepest wells of talent and treasure, have what it takes to succeed. A few small companies have managed to bring some novel compounds out of the lab and into the early stages of human studies, but it appears that economizing in order to keep a drug under a small company's roof too often compromises necessary preliminary research. One pathway for small companies is to license to or partner with major drug makers willing to provide cash and expertise in exchange for an instant pipeline and corporate growth via acquisition or licensing deals.

Bevirimat (PA457) from Panacos is the first-in-class offering of a maturation inhibitor that prevents HIV from correctly assembling itself during the final stages of viral replication. Bevirimat-treated HIV virions are released from infected cells but are unable to successfully infect new cells. While the concept appears sound, the sponsor has had difficulty creating a practical formulation of the product, and clinical trials designed to assess dosages have been held up. Bevirimat is an example of a promising drug that may be significantly delayed or abandoned because a smaller sponsor lacked the resources to solve

the many difficult problems associated with turning a concept molecule into a viable drug candidate.

TNX-355 from Tanox is another novel anti-HIV biologic agent that is quite effective in preclinical studies but presents problems in dosing and administration. The drug is a monoclonal antibody that sticks to the CD4 receptor on T cells and blocks HIV attachment. TNX-355 is administered by intravenous infusion once every one or two weeks. Initial human studies suggested that doses based upon preclinical studies were too low. Consequently, the US Food and Drug Administration (FDA) recommended that the dosing studies be redone. Genentech is seeking to acquire Tanox, and it is not clear whether development of TNX-355 would continue under the new management.

BILR-355 is a new NNRTI under early clinical development by Boehringer Ingelheim. The drug, if not the patient, benefits from co-administration with ritonavir.

A handful of new and recycled NRTIs are being developed by several small companies. Some of these have been in development stasis for several years and none has yet emerged as a high-priority candidate. One hopes that a major sponsor is secretly testing a breakthrough, next-generation NRTI that will leap into the pipeline in the coming year.

Pharmasset is working on **racivir** and **dexelvucitabine (Reverset)**. Racivir has been evaluated in trials for activity against HIV that is resistant to lamivudine. At a dose of 600mg per day, dexelvucitabine would likely be limited to second-line therapy since it is not a candidate for single-tablet combination regimens. Dexelvucitabine showed promise for suppressing HIV that is resistant to several approved NRTIs, but has been sidetracked by concerns about pancreatitis. RFS Pharma is developing **amdoxovir** and its prodrug, both intended to be active against HIV with common NRTI resistance mutations. **Apricitabine (AVX754)** is an NRTI candidate currently being developed by Avexa after earlier efforts by Shire and BioChem Pharma. Apricitabine is designed for activity against NRTI-resistant HIV. Achillion Pharmaceuticals' **elvucitabine**, an NRTI in early clinical studies, may have activity against resistant HIV.

Hepatitis C Virus Pipeline 2007

HCV Drugs in Clinical Trials

Phase II	Phase III

Albuferon: Interferon—*Human Genome Sciences; Novartis*

Locteon: Interferon—*Biolex*

Taribavirin (Viramidine): Ribavirin—*Valeant*

R1626: HCV polymerase inhibitor—*Roche*

HCV-796: HCV polymerase inhibitor—*Wyeth; Viropharma*

NM283 (valopicitabine): HCV polymerase inhibitor—*Novartis; Idenix*

VX-950 (telaprevir): HCV protease inhibitor—*Vertex; Tibotec*

SCH 503034 (boceprevir): HCV protease inhibitor—*Schering*

Celgosivir (castanospermine): Maturation inhibitor—*Migenix*

Bavituximab: Antibodies—*Peregrine Pharmaceuticals*

Civacir: Antibodies—*NABI Pharmaceuticals*

HCV vaccine IC41: Therapeutic vaccine—*Intercell*

GI262570 (farglitazar): Antifibrotic—*GlaxoSmithKline*

PF3491390 (Idun 6656): Antifibrotic—*Pfizer*

DISCONTINUED: GS9132 (ACH806): HCV protease inhibitor—Gilead; Achilon.
Actilon (CPG 10101): Toll-like receptor agonist—Coley; Pfizer.

Unlike HIV treatment, current HCV therapy can actually cure* hepatitis C virus (HCV) infection in some people. Today's standard HCV treatment is based on pegylated interferon (pegIFN) used in combination with ribavirin. The former taps the body's innate capacity to fight viral infections, and the latter may impair the ability of the virus to reproduce.

The many problems with this duo begin with the fact that the cure rate for HCV therapy varies greatly depending on the type of HCV one has

* A sustained viral response is defined as having no detectable HCV six months after treatment has ended. Many regard this as virtual eradication of HCV, or a cure, however liver damage may persist.

and other factors. Under the best circumstances—for HIV-negative people who have non-genotype 1 HCV—cure rates with a pegIFN/ribavirin regimen can exceed 80%. However, genotype 1 HCV, the most difficult to treat—and the most common among people in the United States—is cleared by treatment in less than half of cases. If a person also has HIV infection, that cure rate drops further. For unknown reasons, response rates are poorer among African-Americans.

Another complication is that a typical course of treatment lasts for six months to a year, and then another six months is required to know if the suppression of viral replication seen at the end of treatment will last. People who have not been cured will rarely fare better the second time around.

With several million infections in the United States and at least 130 million worldwide, these low cure rates alone should be enough to trigger a gold rush among pharmaceutical companies to find better HCV drugs. The need is compounded by the profoundly awful side effects of the current regimen. Although pegIFN only needs to be injected once a week, each dose can produce debilitating flu-like symptoms that last for days. Continued dosing often causes serious depression and can dangerously exacerbate a pre-existing mental illness. Ribavirin can cause severe anemia, which saps a person's energy; dose reduction to manage anemia can reduce efficacy. In 2007, successfully completing a course of standard HCV treatment (which does not guarantee a cure) often depends on having excellent support systems, including the careful attention of an experienced physician and nurse to help manage the side effects. Needless to say, these resources are scarce for poor people, drug users, and prisoners—those among whom HCV is most common in the United States and in many other countries.

The main thrust of drug discovery for HCV has been seeking antiviral agents that defeat the virus by inhibiting its essential enzymes. The foremost targets for inhibition have been the HCV protease and polymerase proteins. This approach follows in the successful footsteps of HIV drugs, though the path is not as straightforward. One big difference between developing drugs for HIV and for HCV is the absence of an easy cell-based assay to show whether or not HCV replication

has been stopped by a drug candidate. This results in much more uncertainty about a drug's potency when the decision is made to begin human testing. Even if an HCV inhibitor reduces viral load in a short-term study, there is no way to predict whether it will produce a sustained effect or a cure. The widely varying response rates among different populations with different cofactors (HCV genotype, ethnicity, HIV status) only add to the uncertainty about how best to move these new drugs toward approval. The inclination of drug companies to cherry-pick the easiest-to-treat patients for clinical trials will make it harder to identify a drug that will be effective in the real world. While there are many anti-HCV candidates in early stages of clinical testing, overall progress through the pipeline has been sluggish at best.

As with the HIV drugs, HCV drug resistance mutations have emerged that can thwart the novel anti-HCV drugs tested so far. This suggests that combination therapy—another lesson from HIV—must be adopted if these drugs are to have a shot at producing long-term viral suppression and cure. A real quandary remains: How can you evaluate a drug combination if it does not include an already-proven drug? Also, what if the only viable partner drug belongs to an uncooperative competitor?

A revolutionary advance in HCV treatment would be a minimally toxic drug or drug combination that cures without depending on interferon (IFN) and ribavirin. However, years may pass before the new generation of HCV drugs is ready to stand alone. For the foreseeable future, drug makers are planning to simply replace ribavirin or add an experimental drug to pegIFN/ribavirin to see if cure rates improve. Recent attempts to replace ribavirin have been disappointing, and worse still, it's possible that interferon may prove indispensable. Some scientists speculate that while targeted antivirals may suppress HCV, they may not be able to eliminate it without interferon. Furthermore, even if HCV is not cleared, the health of the liver often improves significantly during the treatment period—an outcome that may be partially attributable to interferon. New HCV antivirals may not yield such beneficial effects.

Given that pegIFN and ribavirin seem entrenched for now, another focus of HCV drug development has been to improve the tolerability

and effectiveness of these agents or possibly shorten the duration of treatment. IFN already underwent a successful iteration recently when the more convenient pegylated formulation replaced the original IFN, which required daily injections. PegIFN also significantly improved cure rates in comparative clinical trials.

The Old Guard

The next few drugs to dribble out of the HCV pipeline may be makeovers of IFN and ribavirin. A more convenient dosing schedule for IFN would be a nice improvement in the lives of people on treatment, but hardly a revolution.

Albuferon from Human Genome Sciences/Novartis is intended to be a kinder, gentler IFN that only requires injection every other week. A phase II study found that patients receiving Albuferon had comparable rates of viral response to patients on weekly pegIFN. Vaguely defined quality-of-life scores also improved, but adverse event rates were similar. A pair of large phase III trials, one for genotype 1 HCV and the other for genotypes 2 and 3, is underway.

Biolex has performed initial clinical safety testing on a controlled-release form of IFN called **Locteon**, which contains the company's **BLX-883** version of interferon. A small study in healthy subjects showed Locteon producing milder flu-like symptoms than pegIFN. A small dose-ranging study is underway and the sponsor recently secured funding to conduct larger efficacy trials.

Taribavirin (formerly viramidine) is a ribavirin prodrug from Valeant currently being compared to ribavirin in a phase II trial, with both accompanied by pegIFN. The great hope with this drug was that it would minimize ribavirin-associated anemia due to its unique mechanism. Two earlier phase III trials found less anemia but also less efficacy than conventional ribavirin. These results sent the drug back to phase II for further dosing studies. The trial currently underway evaluates three weight-based doses.

HCV Polymerase Inhibitors

HCV polymerase is said to be an attractive target for inhibition with small molecules because its binding site is more easily and durably blocked than that of HCV protease.

The three inhibitor drugs in this category are provocative because all are backed by the deep pockets and expertise of major pharmaceutical companies that potentially bring more savvy to drug development than smaller start-up companies can. Roche, already a leader in the $5 billon annual HCV market, would presumably be highly motivated to have another successful HCV product to help secure its position.

All three HCV polymerase inhibitors are at critical stages of development. Their phase II trials are maturing and, if all has gone well, each sponsor should be nearly ready to announce the dose that will be taken forward into larger phase III trials. If these were HIV drugs, no time would be wasted moving them along. But for HCV, the path is not as well marked. When a company delays starting up large, expensive phase III studies, its inaction may represent a lack of confidence in the drug and difficulty in securing commitment and funding within the company. This is also a critical time when toxicity, resistance, or other problems might cause a company to scratch a leading drug candidate and go to the bench for a backup. If the wrong dose range was chosen in phase II testing, or if going without ribavirin turned out to be a bad idea, the drug's developers may need to hold the product back and repeat the second stage of the phase II studies. For the big drug makers, there are contingency plans for such catastrophes, but tiny companies may find these setbacks to be fatal.

HCV-796 from Wyeth/Viropharma is an HCV polymerase inhibitor currently in a phase II study involving 200 to 300 treatment-naïve patients with genotype 1 HCV. The study compares three or more doses of HCV-796 plus pegIFN/ribavirin to standard therapy. A 14-day monotherapy study of HCV-796 produced its maximum viral load reduction at day four, with virus levels subsequently creeping back up, suggesting that resistance to this drug occurs rapidly.

R1626 is the prodrug of an HCV polymerase inhibitor from Roche. A 100-person phase II study (Apollo) is comparing two doses of R1626 plus pegIFN with or without ribavirin. A 14-day monotherapy study reported good viral load reductions within two weeks, although the day of peak response, which may indicate the potential for resistance, was not reported.

NM283 (valopicitabine) from Novartis/Idenix is an HCV polymerase inhibitor paired with pegIFN as a ribavirin replacement in two phase II trials: one for treatment-naïve patients and one for patients with prior treatment failure. Disappointing preliminary results at the end of treatment for the experienced group did not buoy hopes for the early retirement of ribavirin. Study doses of NM-283 were reduced due to gastrointestinal (GI) intolerability.

HCV Protease Inhibitors

HCV protease may be a tougher enzyme to inhibit than the polymerase, but the payoff may be greater if it can be done. Not only is HCV protease essential for viral replication, but some evidence indicates that it also may help defeat one of the body's natural antiviral defenses, the production of endogenous interferon.

VX-950 (telaprevir) from Vertex/Tibotec is currently being studied in three large phase II trials in diverse populations. PROVE 1 and 2 involve 580 treatment-naïve US and European patients with genotype 1 HCV. PROVE 3 aims to enroll 440 previously treated genotype-1 patients who did not achieve a sustained response. A 14-day study demonstrated a rapid initial decline in HCV viral load with rapid rebound in some cases, suggesting the presence of resistant virus at baseline. A subsequent small study demonstrated no viral rebound when VX-950 was administered with pegIFN/ribavirin. Although interim results from PROVE 1 indicated good response rates at week 12 of treatment, the VX-950 groups had more discontinuations due to adverse events—including severe rash, anemia, and GI-related side effects.

SCH 503034 (boceprevir) from Schering is being studied in North America and Europe in HCV SPRINT 1, a 500-person phase II trial in

treatment-naïve patients with genotype 1 HCV. A 350-person phase II trial in patients who did not respond to previous pegIFN/ribavirin treatment is also underway. In a 14-day study in prior nonresponders, SCH 503034 plus IFN lowered HCV viral load more than either IFN or SCH treatment alone.

Other Approaches

Celgosivir from Migenix is a prodrug of castanospermine, a natural compound that appeared in HIV pipeline reports during the early 1990s. Castanospermine did not work against HIV, but the sponsor says results from a small phase II trial in HCV patients who had not responded to previous HCV treatment suggest celgosivir plus pegIFN/ribavirin improved response rates compared to pegIFN/ribavirin alone. However, more patients in the celgosivir arm discontinued treatment due to adverse events. The drug inhibits alpha-glucosidase I, a human protein necessary for viral maturation.

Monoclonal antibodies targeted to HCV may be an expensive but useful therapy for preventing HCV re-infection in liver transplant patients or for providing an immune assist during HCV treatment. **Civacir** from Nabi Pharmaceuticals is currently in a 30-person, randomized proof-of-concept study to determine its impact on liver fibrosis progression and viral load. **Bavituximab** from Peregrine is an antibody targeted to markers on virally infected cells. The product is in very early clinical testing.

Various manufacturers are testing **vaccines** that might help treat and prevent HCV infection. So far, the vaccines furthest along have failed to show convincing efficacy. Intercell expects to report viral load reduction results from phase II proof-of-concept testing of its HCV peptide-based vaccine **IC41** in mid-2007. Novartis, a giant among vaccine makers, is advancing several products through early-stage testing.

Antifibrotic agents are intended to regress liver damage caused by disease. **GI262570 (farglitazar)** from GlaxoSmithKline is being studied in a 225-person placebo-controlled trial to evaluate liver histology

improvement in patients who have previously failed HCV treatment. **PF3491390** from Pfizer is a caspase inhibitor in a phase II trial. The liver has remarkable self-repairing powers, and controlling or curing hepatic viruses that damage the liver often allows significant regression of fibrosis. However, some scientists doubt that these agents can help the process.

Tuberculosis Pipeline 2007

Phase II	Phase III	Phase IV

TB Drugs in Clinical Trials

Isoniazid (INH) preventive therapy: Antibiotic—*Aurum; CREATE; JHU; RJ*

INH + rifapentine preventive therapy: Antibiotics—*JHU; PHRU; TBTC*

INH + rifampin preventive therapy: Antibiotics—*JHU; PHRU*

Gatifloxacin (G): Fluoroquinolone—*EU; IDR; TDR; Lupin*

Moxifloxacin (M): Fluoroquinolone—*Bayer; JHU/TB Alliance; TBTC; UCL*

TMC207 (J): Diarylquinoline—*Tibotec*

OPC-67683 (O): Nitroimidazo-oxazole—*Otsuka*

TB Vaccines in Clinical Trials

MVA85A: Modified vaccinia virus Ankara (MVA) plus antigen—*Oxford*

CREATE = Consortium to Respond Effectively to the AIDS/TB Epidemic; EU=European Union; JHU = Johns Hopkins University; IRD = Institut de Recherche pour le Développement; PHRU = Perinatal HIV Research Unit; RJ = Rio de Janeiro municipal government; TBTC = TB Trials Consortium; TDR = Special Programme for Research and Training in Tropical Diseases; UCL = University College London.

In the static world of TB research, decades seem to tick by with no evident progress in diagnostics, vaccines, or treatments. Rip van Winkle would feel right at home in a world where the most widely used TB diagnostic (the microscopic smear) was introduced in 1882, the last TB vaccine (BCG) in 1921, and the anchor drug in first-line therapy (rifampin) in 1963. This is in stark contrast to HIV research, where nearly each new year brings a new drug to the market. The US National Institutes of Health (NIH), the world's biggest funder of biomedical research, allocates to TB only 5.4% of the amount it spends on HIV/AIDS research ($158 million versus $2.9 billion in 2005).

According to the World Health Organization (WHO), 8.8 million new cases of TB and 1.6 million deaths occurred in 2005. Yet WHO-recommended standard national TB programs failed to detect 47% of all new

TB cases in 2005. This is due to incomplete access to TB programs and to the insensitivity of the most widely used diagnostic test, sputum smear microscopy. Of the 1.6 million deaths, about 195,000 were among HIV-infected persons. In some countries, such as Swaziland, people with HIV infection account for as many as 75% of TB cases. Scandalously, just 4% of all HIV-infected persons with TB were put onto antiretroviral therapy in 2005, according to WHO, and <0.1% of HIV-infected adults in Africa received TB preventive therapy.

A new TB treatment should do at least one and optimally all of the following:

- Decrease the duration and pill burden of treatment;
- Have manageable interactions with anti-HIV drugs;
- Improve and/or shorten treatment for latent TB infection;
- Treat multi- and/or extensively drug resistant TB; and
- Treat pediatric TB.

Treatment for Latent TB Infection

People who carry the TB bacillus but do not have active disease have latent TB infection (LTBI) and should be treated to prevent subsequent reactivation and onward transmission. The current standard of care for treating latent TB is a six- to nine-month course of isoniazid (INH), which patients often fail to complete. A number of existing regimens—including isoniazid, rifampin, rifapentine, and some combinations—are being examined in multiple populations for varying lengths of time to see whether treatment for latent TB infection can be shortened or improved.

Although treatment of LTBI will be essential to ultimately eliminating TB, little effort is being focused on improving preventive therapy for drug-susceptible TB. Furthermore, there are no efforts at all to use novel agents as preventive therapy to avoid active disease in persons exposed to infectious cases of multi- and/or extensively drug resistant TB (M/XDR-TB).

Past studies clearly demonstrate that INH preventive therapy (IPT) reduces incidence of TB disease in HIV-infected persons by 60-90%

among those with a positive TB skin test. The rate is 36% when individuals who do not have latent TB infection are included. Potent antiretroviral therapy (ART) can also reduce TB incidence by up to 80% among HIV-infected persons. However, the risk of TB still remains elevated in individuals receiving ART, and TB is now the most common opportunistic disease among those on ART in both developing and developed countries. The fact that people with HIV often live in high TB prevalence areas makes it difficult to assess the optimal duration of INH prophylaxis, since re-infection or re-activation of TB may occur among those living longer due to ART.

Two large current studies are likely to have important implications for people living with HIV. If effective, the study interventions can be implemented rapidly, since both studies use readily available INH for the prevention of TB.

The Thibela-TB study is a very large trial which aims to combat TB in South African gold mines where the annual incidence of TB disease is 4% and where HIV rates are also very high. This study will randomize all employees within an entire mine shaft to receive either nine months of **isoniazid (INH)** given with **folic acid (B12)** to prevent neuropathy or to the standard of care, which is INH for those individuals who are found through voluntary HIV counseling and testing to be HIV-positive. The study is being conducted by the Aurum Health Research Institute at 16 mine shafts owned by three mining companies, with funding coming from the Bill & Melinda Gates Foundation via the Consortium to Respond Effectively to the AIDS-TB Epidemic (CREATE) at Johns Hopkins University. Approximately 30,000 mine workers in eight mine shafts will be randomized to receive mass INH preventive therapy, with a similar number from the other eight shafts comprising the control arm.

A second large randomized community study sponsored by CREATE is THRio, which involves HIV-positive patients taking ART at 29 clinics in Rio de Janeiro. The clinics will be randomized to implement IPT (the rarely-practiced national Brazilian policy) in phases, and the impact on TB rates will be examined.

TB Trials Consortium (TBTC) Study 26 is a 7,700-person study comparing nine months of daily INH (270 doses) to three months (twelve doses) of weekly **INH with rifapentine** (a rifamycin that has a longer half-life than rifampin). The goals are to prevent disease in people with latent TB infection, including children and people who have HIV, and to see whether the shorter two-drug course is as effective as the standard of care. Results are expected in December 2010. Of 6,900 people currently enrolled, however, fewer than 200 are HIV infected.

A study cosponsored by the US Centers for Disease Control and Prevention (CDC) is comparing 6 to 36 months of **INH** in 2,000 HIV-infected adults in Botswana.

A 1,148-person trial cosponsored by Johns Hopkins University is comparing four regimens to prevent TB disease among HIV-infected, PPD-positive adults in Soweto, South Africa. The four regimens are **rifapentine/INH** weekly for 12 weeks; **rifampin/INH** twice weekly for 12 weeks; INH daily for life; and INH daily for six months.

Three reasons are normally given for the failure of public health programs to implement IPT despite overwhelming evidence of its efficacy:

1. It is too hard to rule out active TB among HIV-infected persons;
2. Adherence to IPT is poor; and
3. IPT may cause outbreaks of INH-resistant TB due to poor adherence.

These are poor excuses. All HIV programs should be implementing the WHO-recommended collaborative HIV activities, including active case finding for TB, as well as IPT for those without active TB disease. New WHO guidelines, *Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary TB among adults and adolescents*, provide an updated framework—including earlier use of chest X-rays, laboratory cultures, and HIV testing—for more aggressive case finding for TB.

Adherence to IPT can easily be improved with the involvement of community-based treatment supporters, as is widely done with ART for HIV.

Finally, there is no evidence that INH preventive therapy increases the risk of clinically significant INH resistance which would preclude a subsequent successful response to four-drug first-line TB therapy.

First-Line Therapy and Treatment-Shortening Regimens

The bar is set high for a new first-line TB treatment regimen. In a well-run program—rarely attained in many parts of the world—cure rates are 95% or more for treatment of drug-sensitive TB (the vast majority of cases) with two months of isoniazid (H), rifampin (R), pyrazinamide (Z), and ethambutol (E) given daily followed by four months of isoniazid/rifampin (HR), often given three times per week. A new curative regimen would need to exceed 95% efficacy or offer a major advantage in terms of treatment shortening (e.g., four months of treatment rather than six). Even then, TB programs would be unlikely to adopt a shorter regimen if it reduced cure rates.

Nonetheless the need for shorter treatment regimens is urgent. Only 19% of cases are detected by today's most widely used TB diagnostic, smear microscopy, and fewer than half of cases would be detected by it in the best run laboratories. Similarly, though current first-line therapy is highly effective, many people in real-world circumstances fail to complete treatment, missing out on a chance to be cured. These people may later present with recurrent disease, and sometimes develop drug-resistant TB, which is much harder to treat. Thus, a shortened first-line treatment regimen could improve clinical outcomes just by reducing the numbers of defaulters on treatment and losses to follow-up.

An additional problem is posed by the significant drug-drug interactions between rifampin—the foundation of first-line TB therapy—and many first- and second-line antiretroviral therapies (ART). Nevirapine and efavirenz, which together anchor most scale-up programs in the developing world, are particularly problematic. While a growing body of data indicates that these drugs may be acceptably safe in combination with rifampin, this is not the case with ritonavir-boosted protease inhibitors (bPIs), which WHO recommends as the foundation for second-line ART. As greater numbers of individuals benefit from ART scale-up, some will inevitably fail on first-line therapy and need to go onto a bPI such as

lopinavir/ritonavir. If these individuals then develop TB they will be in a tight spot, forced to choose between two life-saving treatments.

Two fluoroquinolones—a class of broad-spectrum antibiotics widely used around the world to treat a range of infections—are the most advanced candidates for potentially shortening the duration of TB therapy while preserving high cure rates. Varying levels of resistance to fluoroquinolones already exist in many places. **Gatifloxacin** and moxifloxacin are currently in phase II and III studies for shortening first-line therapy regimens. Gatifloxacin is being studied by a European Union-funded consortium to replace ethambutol in the intensive phase of treatment. Even if gatifloxacin succeeds in allowing a shorter (four-month) first-line therapy regimen, it is unlikely to be widely adopted due to severe adverse events seen in a 2006 trial. Nonetheless, demonstrating the viability of a four-month fluoroquinolone-based regimen would be an important step forward. Study completion is expected by December 2008.

Moxifloxacin has been shown in a TBTC study to be at least equivalent to ethambutol during the two-month intensive phase of treatment, and is now being compared with isoniazid in another phase II study. Enrollment is completed and preliminary results are expected in July 2007. A parallel study is underway in Brazil, sponsored by Johns Hopkins University and supported by the FDA.

The 1,500-person phase III ReMox study, which will compare two four-month regimens with the six-month standard, will open enrollment in Kenya, South Africa, Tanzania, and Zambia in the third quarter of 2007.

MultiDrug-Resistant and Extensively Drug-Resistant TB

Up to 10% of TB cases worldwide are believed to be resistant to at least one of the four first-line drugs. TB that is resistant to the two most important ones, isoniazid and rifampin, is designated as multi-drug resistant (MDR). Treatment for MDR-TB requires using a greater number of less effective drugs with increased side effects, for much longer periods, in order to treat and cure a much smaller proportion of

those infected. Many countries use a standardized MDR-TB regimen; in the case of South Africa this includes four months of treatment with five drugs, including an injectable aminoglycoside (kanamycin) plus ethionamide, pyrazinamide, a fluoroquinolone (usually ofloxacin), and ethambutol (if the strain is still sensitive) or terizodone.

South Africa has a high rate of treatment failure even for first-line therapy (30%) and high rates of default or transferring out of TB programs, resulting in a large and growing MDR-TB epidemic. The crisis has recently captured the world's attention due to the emergence of a TB strain resistant not only to isoniazid and rifampin but to several of the most important second-line drugs, including a fluoroquinolone and at least one injectable (amikacin, capreomycin, or kanamycin). Every country which conducts drug resistance surveillance has reported this kind of TB, dubbed extensively drug-resistant (XDR) TB. It is especially deadly among people with HIV: In a rural KwaZulu Natal (South Africa) hospital, 98% of patients died a median of 16 days after sputum was collected, usually many weeks before the diagnosis of XDR-TB was established.

Even in the best of circumstances, only about 30% of people with XDR-TB are cured. Unlike South Africa, most countries with high HIV prevalence, especially those in Africa, lack even the laboratory infrastructure necessary to diagnose M/XDR-TB. Cases simply go undetected, or are recorded as regular TB cases and deaths. WHO estimates that worldwide there are approximately 425,000 new cases and 116,000 deaths caused by MDR-TB each year and that there are 27,000 new cases and 16,000 deaths annually from XDR-TB. However, in the absence of a massive scaling up of laboratory infrastructure to detect, diagnose, and treat these drug-resistant TB cases, we are completely in the dark about the true magnitude of the problem. Recent recommendations by WHO to dramatically and rapidly scale up access to TB culture technology and drug susceptibility testing in high-burden countries are a step in the right direction, but will require $2 billion in the next two years to achieve predicted results.

No one was developing drugs for MDR-TB until recently, and TB traditionalists scoffed at the notion of controlled clinical trials in such a heterogeneous, putatively difficult-to-treat population. At a Médecins sans Frontières (MSF) TB research and development symposium in New York City in January 2007, however, a consensus emerged that TB researchers could take a page from the book of HIV salvage therapy research and test new drugs against optimized background therapy.

Tibotec/J&J's diarylquinoline **TMC207** (a.k.a. "**the J drug**") is one of the few products steadily advancing through the clinical pipeline. The sponsor decided to postpone studies of the drug's potential for first-line therapy because an interaction with the key first-line drug rifampin lowers blood levels of TMC207 by 50%. Food increases absorption two-fold. Researchers have completed a seven-day early bactericidal activity (EBA) study of the drug at 25, 100, and 400mg daily versus isoniazid/rifampin. Steady-state levels were not reached in seven days.

Tibotec/J&J is planning an innovative 200-person phase II study of TMC207 plus standard background regimen (SBR) versus SBR alone for the treatment of MDR-TB in South Africa. The study will be the first-ever trial of a new TB drug for MDR-TB intended to be submitted to regulatory authorities for approval, a move for which Tibotec/J&J should be commended. A better treatment regimen for MDR-TB could forestall the development of XDR-TB.

Otsuka's nitroimidazo-oxazole **OPC-67683** has completed EBA studies and an exploratory five-arm 54-person trial in South Africa. Further phase II studies are likely. It is unclear whether this drug will be studied first in drug-sensitive or drug-resistant TB.

NIH-funded researchers are looking at an approved drug, **linezolid** (marketed by Pfizer as Zyvox for treatment of drug-resistant *S. aureus* and streptococci), in an EBA study, and linezolid is being considered for treatment of XDR-TB. However, a 2007 FDA alert warned that "patients treated with linezolid had a higher chance of death than did patients treated with any comparator antibiotic." Unless safer effective doses can be defined, this drug is unlikely to be widely used except for cases of MDR- and XDR-TB.

Early Phase Clinical Trials

The TB Alliance's nitroimidazo-oxazine, PA-824, has recently completed phase I development in healthy volunteers and is expected to enter an EBA study in August 2007. Following single- and multiple-ascending dose studies, a transient elevation in a single kidney function marker (serum creatinine, but not BUN) was noted. Further investigation of this unexpected event was deemed necessary, slowing down the next phase. However, a dedicated renal effects study was recently concluded, and it suggested that PA-824 does not have any deleterious effects on kidney function, but rather causes an isolated, reversible elevation of serum creatinine. If EBA studies begin on schedule, TB patients will receive this drug for the first time in August 2007.

Lupin Pharma's pyrrole **Sudoterb (LL-3858)** has entered clinical studies. With nothing published in the peer-reviewed literature, little is known about this compound.

Sequella's diamine compound **SQ109** entered phase I last fall with a good deal of fanfare, at least on the company website. It is a member of the same chemical family as ethambutol but may have activity against ethambutol-resistant *M. Tb*.

Scientific evidence suggests that sunlight (part of the century-old TB sanatoria regimens) may be beneficial partly because it induces endogenous vitamin D production. The Christian Medical College is planning a randomized, double-blind, placebo-controlled study of supplemental **vitamin D** plus anti-TB therapy in South India.

Empty Preclinical Tributaries

Despite a good deal of optimistic prose, the preclinical TB drug pipeline is not robust, as MSF pointed out in a cautionary report last November. Otsuka and Tibotec both apparently have backup compounds ready for EBA studies, but most other information in the public domain suggests that other companies and the TB Alliance are still in the discovery phase. Two exceptions: a Harvard team is looking at aerosolizing capreomycin (an M/XDR drug), while a team from Colorado is examining aerosolized rifamycins in mice.

Poor TB Clinical Trials Infrastructure

Less than $50 million is being spent on randomized phase II/III TB treatment trials worldwide, and all such trials currently open are looking at only one class, the fluoroquinolones.

The largest single TB clinical trials organization in the world, the CDC-funded TBTC, has endured years of funding cuts. TBTC is only slated to receive $9 million in 2007 despite the newly emerging threat of M/XDR-TB and the greater number of new candidates to study. Meanwhile, the TB Alliance, which last year received a five-year, $104 million grant from the Bill & Melinda Gates Foundation, is currently funding only early-stage studies of PA-824 and contributing to the moxifloxacin studies described above. The philosophical commitment to studying new M/XDR-TB drugs is not matched by adequate resources, except in the unusual case of Tibotec/J&J.

We desperately need more resources for clinical trials infrastructure, training, and intensified research into biomarkers and diagnostics. Without major improvements, even today's deeply inadequate TB drug pipeline cannot be rapidly advanced in a coordinated fashion to bring new drugs and shorter, safer, and more effective combination regimens into clinical practice.

TB Vaccines

The current TB vaccine, bacillus Calmette-Guérin (BCG), is given to approximately 100 million newborn infants each year. Initially grown as an attenuated form of *Mycobacterium bovis* in 1908 by Albert Calmette and Camille Guérin at the Institut Pasteur in France, the vaccine has continued to evolve and it is believed that there are significant genetic and immunologic differences between various currently available strains (e.g., Brazilian, Danish, Japanese). While never universally adopted and never the standard of care in the Netherlands or the United States, BCG has been widely used around the world. A meta-analysis published in 2006 estimated that in each yearly cohort of 100 million babies immunized, BCG may prevent about 30,000 cases of TB meningitis and 11,000 cases of miliary (disseminated)

TB. It is believed that BCG also induces a useful Th1 type immune response among vaccinated newborns, which may strengthen resistance to other infectious diseases.

BCG's efficacy is variable and incomplete, and probably does not protect most older children, adolescents, and adults from reactivated, pulmonary, or extrapulmonary TB. Unlike many other vaccines, BCG does not appear to be improved by boosting with additional doses.

An ideal new TB vaccine would build on BCG's protective effects on infant miliary TB and TB meningitis; protect from reactivation of latent disease or reinfection; prevent pulmonary and extrapulmonary TB disease in older children, adolescents, and adults; protect against TB among the immune suppressed, including people with HIV; and provide protective immunity by acting as a therapeutic vaccine when given post-infection to those with latent infection and active disease.

A few global multidisciplinary efforts are underway to develop a more effective TB vaccine, many of which are being coordinated by the Aeras Global TB Vaccine Foundation. Headquartered in Rockville, Maryland, and funded by a variety of partners, chief among them the Gates Foundation, Aeras has—unusually for a product development partnership—built an in-house factory, giving it the ability to manufacture 150-200 million doses of recombinant BCG (rBCG) per year. This technology can also be used to make other vaccines. The philosophy of Aeras, according to CEO Jerald Sadoff, is to build on the already proven efficacy of BCG. The strategy: add immunogenic TB proteins to make recombinant BCG, and/or use TB proteins with adjuvants or other bacterial or viral vectors expressing TB proteins as boosters to increase and broaden the immunity provided by BCG.

While few candidates are yet in the clinic, Aeras has a portfolio of six lead candidates (one for priming and five for boosting), and has already established a global platform and strong partnerships to carry the research forward. With support from Aeras, Greg Hussey and colleagues at the South African Tuberculosis Vaccine Initiative recently completed a huge five-year study in a rural, low-HIV-prevalence region in Western Cape Province, South Africa. The study compared percuta-

neous Japanese BCG to intradermal Japanese BCG among 11,800 South African neonates to see whether BCG is equally immunogenic by both routes. The outcome: no overall differences in TB incidence.

Aeras is also sponsoring large-scale epidemiological work in India to pave the way for eventual efficacy trials there.

One approach being studied by Oxford University is modified vaccinia virus Ankara (MVA) encoding a secreted antigen from *M. tb.*, antigen 85A. Phase I studies of this construct, known as **MVA-85A**, have been completed in healthy volunteers. A phase I study among HIV-infected individuals is currently enrolling participants, as is a larger (500 person) study. A phase II study among HIV- and TB-uninfected adults in South Africa is currently underway, and a small study in asymptomatic persons infected with either TB, HIV, or both is scheduled to open this summer, also in South Africa.

Another viral vector in early phase I trials is AERAS-402, using the AdVac vaccine technology from Crucell. This product addresses a potential pitfall of the Merck and NIH Vaccine Research Center (VRC) adenovirus 5 (Ad5) vectors now being used in large phase IIb HIV vaccine studies. Because Ad5 is common in the environment, many people have high levels of pre-existing immunity to it. Therefore AERAS-402 is using the much less common adenovirus 35 strain, which may deliver the same immunologic effect when administered at lower doses. Aeras and Crucell are collaborating on two phase I trials of AERAS 402, the first in the US and the second in South Africa, using the AdVac approach.

A phase I trial of a TB nasal subunit vaccine candidate called **Ag85B-ESAT6** opened in January 2007 at St. George's Vaccine Institute University College London. The six-arm, 42-person study, sponsored by the European Union in collaboration with Novartis Vaccines and Statens Serum Institut, will evaluate Ag85B-ESAT6 given nasally with or without the LTK63 adjuvant in two doses two months apart. Participants will include BCG-exposed and non-BCG-exposed healthy adults.

Assuming any of these early candidate TB vaccines move toward randomized, controlled phase II/III efficacy trials, the remarks made

above concerning the need to continue and expand development of an effective global TB clinical trials infrastructure will come to the fore. Two large-scale efficacy trials of a pediatric regimen and an adolescent booster are likely to cost at least $120 million, which is $50 million more than the world currently spends each year on all TB vaccine research combined.

All told, the present global investment in TB research and development, including discovery and development of new drugs and new vaccines, is woefully disproportionate to the scale of the problem. Global leaders have failed to rise to the challenge posed by the Stop TB Partnership's *Global Plan to Stop TB: 2006-2015*, let alone the challenge of XDR-TB in South Africa and now in the United States. We lack the diagnostics, drugs, and vaccines to effectively control the disease, let alone to eliminate it by 2050, which is the stated (and, given current investment, unrealistic) goal of the *Global Plan*.

***

To accelerate discovery and development of the full array of new tools required to eliminate TB—vaccines, drugs, and diagnostics alike—annual investment in TB research needs to increase from $400 million to $2 billion per year.

Immune-Based Therapies and Preventive Technologies Pipeline

By Richard Jefferys

In 2007, the landscape for immune-based HIV therapies and preventive technologies (vaccines, microbicides, and pre-exposure prophylaxis [PrEP]) remains rocky and treacherous. Preventive vaccine researchers have a clear idea of their immediate path—evaluating T cell-based HIV vaccines for efficacy—but it is uncertain whether this path will lead to friendlier terrain or end in a precipice, with no neutralizing antibody-based approaches at hand to serve as a safety net. The microbicide field has had to deal with the early termination of two efficacy trials of a product called Ushercell due to an excess of HIV infections among recipients at some of the participating research sites; an investigation of the outcome is underway. Another efficacy trial of the surfactant microbicide Savvy was stopped in September 2006, not due to safety issues but because the compound lacked any protective effect. Two PrEP trials are ongoing and a third efficacy study among Peruvian gay men is about to begin enrolling. Immune-based therapies for HIV infection remain at the margins, with the exception of the cytokine IL-2, which—as the subject of two large international clinical trials, now in their seventh year with no end in sight—appears to have carved out a big, bold road to nowhere.

HIV Vaccines Pipeline 2007

HIV Vaccines in Clinical Trials

Phase II	Phase III
ALVAC vCP1521: Canarypox—*Aventis Pasteur*	
AIDSVAX B/E: Protein—*VaxGen*	
MRK Ad5 trivalent: Adenovirus—*Merck*	
VRC HIV DNA 016/Ad5 boost: DNA plasmids—*NIH Vaccine Research Center*	
ALVAC vCP1452: Canarypox—*Aventis Pasteur*	
LIPO-5: Lipopeptides—*ANRS; Aventis*	
tgAAC09 AAV: Parvovirus—*Targeted Genetics; IAVI*	
ISS P-001: Tat protein—*ISS; ICAV; AIDS Vaccine Integrated Project*	

For all its complexity, HIV vaccine research has followed a relatively straightforward narrative arc. The idea in the 1980s was that vaccines worked primarily via the induction of antibodies, and for a time it seemed that HIV would be susceptible to antibody-mediated neutralization. Researchers hoped that constructing a vaccine would be relatively simple. As it turned out, laboratory-adapted HIV strains had led them astray. The laboratory viruses were easy to neutralize, but those taken directly from infected individuals—dubbed primary isolates—were highly resistant to antibodies. The relevance of these observations to the real world was confirmed earlier this decade by the failure of an antibody-based vaccine called AIDSVAX in two large efficacy trials.

The difficulty of generating effective neutralizing antibodies led the vaccine field to focus instead on T-cell responses. Studies of individuals who remain uninfected after repeated exposure to HIV and of HIV-infected individuals who do not progress to immunodeficiency (long-term nonprogressors), along with research in animals models, suggested that CD8 T-cell responses may play a key role in battling HIV. However, designing vaccines to induce HIV-specific CD8 T-cell

Evaluating T-cell Immunogenicity

Over the past decade, a number of new assays for evaluating T-cell responses have been developed. These assays have proven vital for measuring the immunogenicity of the current crop of T cell-based HIV vaccines. The assays include:

ELISpot (Enzyme-Linked ImmunoSpot), a test that measures the ability of T cells (CD4, CD8, or both) to make cytokines when exposed to a given antigen. T cells are first exposed to the antigen, then antibodies that bind to a specific cytokine are introduced 6 to 24 hours later. The cells are chemically treated so that any antibodies bound to cytokine-producing cells are stained blue and can be counted. (These cells are called "spot-forming cells," or SFC). Background cytokine production (i.e. production that occurs without any antigen stimulation) can be a problem, and must be subtracted to get an idea of how many T cells were specifically responding to the antigen.

Intracellular Cytokine Staining (ICS), which also measures the ability of T cells (CD4, CD8, or both) to make cytokines when exposed to a given antigen. Unlike ELISpot, this test employs a substance that traps the cytokine within the T-cell, allowing easier identification of the precise type of T-cell that is making a given cytokine.

Initially, the cytokine most commonly measured in these assays was interferon gamma. Over the past year there has been an explosion in the use of ICS combined with multiparameter flow cytometry to assess expression of multiple cytokines, chemokines, and other functional markers (particularly CD107a, a marker of a T cell's cell-killing ability). Recent data demonstrate an inverse correlation between the number of HIV-specific T cells capable of multiple functions and the viral load in infected individuals. These "polyfunctional" T cells produce a much greater quantity of cytokines on a per-cell basis than other T cells. The highly efficacious vaccinia virus vaccine has also been shown to induce a polyfunctional CD8 T-cell population, suggesting that such cells play an important role in vaccine-induced protection.

responses turned out to be a challenge. Until just after the turn of the millennium, no HIV vaccine candidate had managed to reliably induce HIV-specific CD8 T-cell responses in more than a third of recipients.

But over the past seven years, researchers finally have been able to address this problem with the advent of new vaccine platforms—particularly vaccines based on adenoviruses. The denouement is that there are now several experimental HIV vaccines that can trigger the development of robust and sustained HIV-specific CD8 T-cell responses in the majority (~60-80%) of recipients. One such adenovirus-based vaccine, developed by Merck, is the subject of an ongoing efficacy trial with 3,000 participants. A second candidate developed by the NIH's Vaccine Research Center (VRC), employing a DNA vaccine as a priming immunization followed by an adenovirus boost, is about to enter an 8,500-person efficacy trial.

These studies represent a critical milestone for the HIV vaccine field. At all stages of development, the vast majority of HIV vaccine candidates are designed to induce T-cell responses. If the Merck and/or VRC products demonstrate some significant degree of protection—either against acquisition of HIV infection or progression to AIDS—there will be the potential for improvement and even licensure sometime in the next decade (depending on the degree of success achieved). But if both vaccines fail, the prospects for all T cell-based approaches will dim and the field will need to turn back to neutralizing antibodies.

Although there has been progress in elucidating the mechanisms by which HIV shucks off an antibody attack, researchers are still a long way from designing a vaccine that can induce effective neutralizing antibodies against HIV. The existence of several monoclonal antibodies with neutralizing activity against a broad array of HIV isolates has long been considered encouraging, but recent data demonstrate that these antibodies can have their limitations when it comes to neutralizing the viruses found in recently infected individuals. A consortium of scientists (the Neutralizing Antibody Consortium) was formed by the International AIDS Vaccine Initiative (IAVI) in 2002 to address this problem, and the group continues trying to find broadly neutralizing antibodies and the means to induce them via vaccination.

Beyond T cells and antibodies, other novel approaches might include the induction of antibodies that block the interaction between the human CCR5 protein and HIV. Another possibility is the development of live replicating vaccine vectors aiming to mimic the robust protection obtained with live attenuated SIV vaccines in the macaque model. (IAVI has a separate consortium working on issues relating to live attenuated vaccines.) However, as is the case with neutralizing antibody-based vaccines, none of these potential novel approaches are likely to be ready for efficacy testing within the next decade. In sum, if T cell-based vaccines fail, the timeline for the development of an effective HIV vaccine is anyone's guess.

Ideal Elements of Vaccines

The ideal vaccine would be safe, affordable, and easy to administer (e.g., a single shot). It would deliver long-lasting immunity, with efficacy against multiple HIV subtypes and complete protection against HIV infection in as many recipients as possible. It also would be easy to manufacture on a large scale, and to ship and distribute globally.

Adenovirus-Based Vaccines. Two vaccine approaches currently in efficacy trials both utilize attenuated forms of adenovirus serotype 5 (Ad5) as a vaccine vector. Adenoviruses are common in nature and cause severe colds; serotypes define different subgroups of adenoviruses based on the antibodies they induce. A feature of adenoviruses that makes them ideal vaccine vectors is their targeting of dendritic cells, which are responsible for initiating T-cell responses.

Merck's Ad5-based vaccine (MRKAd5) encodes the Gag, Pol, and Nef proteins from HIV. There are now two ongoing efficacy trials of this vaccine: a 3,000-person study in regions of the world where HIV subtype B is prevalent (this trial started in 2005) and a recently initiated 3,000-person study in Africa, where HIV subtype C predominates. Results are anticipated by 2010. The VRC's Ad5 vaccine candidate consists of four separate vectors encoding a Gag/Pol fusion protein derived from subtype B HIV and three different Env proteins from subtypes A, B, and C. The VRC is employing this Ad5 vector as a booster following immunization with a DNA vaccine which encodes

the same proteins plus subtype B Nef. Encouraging immunogenicity data from a few early trials has now been published. The VRC's DNA prime/Ad5 boost approach is entering a phase IIb efficacy trial, PAVE 100, which will enroll 8,500 participants. Results are anticipated by 2011.

Unfortunately, because Ad5 is present in the environment, a significant number of people have been exposed to it and possess high levels of anti-Ad5 neutralizing antibodies. In response to this potential problem, several alternate adenovirus vectors are being developed. These include two adenoviruses from less prevalent serotypes (Ad35 and Ad26), a chimeric vector comprised of Ad5 with the highly variable region replaced with components from the rare Ad48 serotype, and a chimpanzee adenovirus. The chimpanzee adenovirus vector is being developed by IAVI in partnership with GlaxoSmithKline.

ALVAC from Sanofi Pasteur is an HIV vaccine candidate that uses a bird virus called canarypox as a vector. Unfortunately, ALVAC induces persistent HIV-specific CD8 T-cell responses in just 10% to 20% of recipients, leading to considerable skepticism about its potential efficacy.

A version of ALVAC is undergoing an efficacy evaluation in a 16,000-person Thai trial initiated by researchers affiliated with the US Military HIV Research Program. The trial is fully enrolled and a Data Safety Monitoring Board (DSMB) review is scheduled to take place in July 2007. It is possible that the incidence of HIV infection in the study population will be too low to determine efficacy, in which case the trial may be stopped on the basis of futility. If the DSMB allows the study to continue, results should be available within three years.

Modified Vaccinia Virus Ankara strain (MVA) is an attenuated, nonpathogenic derivative of the cowpox virus. Initial results with MVA vectors suggested they may be no more immunogenic than ALVAC. In 2006, however, researchers from the Karolinska Institute in Sweden reported impressive immunogenicity results from a DNA/MVA vaccine combination delivered intradermally (into the skin) using a needle-free device called a Biojector. Over 90% of participants in this phase I study developed HIV-specific T-cell responses. The Karolinska Institute and the US Military HIV Research

Program are now advancing this vaccine approach into phase II studies. Three other MVA-based HIV vaccine candidates (manufactured by Therion, Aaron Diamond AIDS Research Center, and GeoVax) are also in human studies.

DNA Vaccines. In the early 1990s, vaccine researchers were surprised to discover that simply injecting DNA sequences encoding protein antigens could induce substantial immune responses in mice. For a time there was much excitement about the potential of these "naked DNA" vaccines, particularly because they are extremely cheap and easy to produce. However, as studies escalated into larger animals and humans, it quickly became apparent that the immunogenicity of the vaccines declined dramatically in these settings. Several candidates abjectly failed to induce detectable immune responses in humans.

Nevertheless, researchers have continued seeking to improve DNA vaccine immunogenicity, and the previously described phase I trial results suggest that HIV DNA vaccines delivered using a Biojector may be a viable component of a prime-boost vaccine regimen. Another promising approach is the use of electroporation, which involves delivering a brief electrical charge to the muscle into which the DNA vaccine is injected. The electricity opens transient pores in local cell membranes, allowing the DNA vaccine easier access to the cell nucleus, where it produces vaccine-encoded antigens. Electroporation also attracts inflammatory cells—including antigen-presenting dendritic cells—to the immunization site. Wyeth has recently published promising animal data on this approach, and human trials are imminent.

Recombinant Proteins. Several vaccine candidates undergoing human trials use recombinant protein components. Chiron is employing an oligomeric envelope protein (gp140, with the V2 region deleted) as a booster following immunization with a DNA vaccine. Macaque studies demonstrated induction of antibodies capable of some degree of neutralizing activity against four of five primary HIV isolates tested, but this activity was seen only at high antibody concentrations. Maverick Italian researcher Barbara Ensoli has long been pursuing the hypothesis that a recombinant HIV Tat protein could

prove effective as a vaccine. Phase I human trials of the vaccine have been completed and phase IIa studies are now being planned for both Italy and Africa.

Adeno-Associated Virus (AAV) is a parvovirus that depends on adenovirus to replicate; the vector has been further modified so that it is completely replication-incompetent. However, recently presented human immunogenicity data have been extremely disappointing, with HIV-specific T-cell responses detected in only 5 out of 25 recipients of the highest dose. An explanation may lie in the recent finding that most humans—unlike macaques—possess CD8 T-cell responses specific for the AAV capsid due to prior exposure; these responses may clear the vector too rapidly for it to be effective.

PrEP & Microbicides Pipeline 2007

Phase II	Phase III

Other Prevention Technologies in Clinical Trials

Pre-Exposure Prophylaxis (PrEP)

Tenofovir (Viread): Antiretroviral—*Gilead*

Tenofovir/FTC (Truvada): Antiretroviral—*Gilead*

Microbicides

Carraguard: Barrier (adsorption inhibitor)—*Population Council*

PRO 2000: Barrier (adsorption inhibitor)—*Indevus Pharmaceuticals*

BufferGel: pH buffer/barrier—*Reprotect*

Tenofovir DF: Antiretroviral—*CONRAD; Intl. Partnership for Microbicides*

TMC 120 (daprivirine): Antiretroviral—*Intl. Partnership for Microbicides*

VivaGel (SPL 7013): Fusion inhibitor—*Starpharma*

DISCONTINUED: Cellulose Sulphate (Ushercell): Barrier—CONRAD. Savvy: Surfactant—Cellegy.

Pre-Exposure Prophylaxis

Pre-exposure prophylaxis (PrEP) is the prophylactic use of antiretroviral drugs to prevent HIV infection. Currently two drugs are being evaluated in phase II studies as PrEP: the nucleotide reverse transcriptase inhibitor tenofovir (Viread) and a combination pill called Truvada, which contains tenofovir and the nucleoside reverse transcriptase inhibitor emtrictabine (Emtriva).

Initial efforts to evaluate the efficacy of tenofovir as PrEP failed due to controversies over trials in Cambodia and Cameroon, along with administrative issues relating to another trial in Nigeria. One study was completed in Ghana, but the number of participants precluded an analysis of efficacy. (There were six infections among placebo recipients and two in the group receiving tenofovir, a non-significant differ-

ence.) No serious safety issues emerged, although there was one case of a grade 3 decrease in phosphorus in a tenofovir recipient, which resolved within 3 months. One participant in the interrupted trial in Cameroon developed elevated liver function tests after drug withdrawal which normalized within a month; this could relate to the concern that tenofovir's activity against hepatitis B may lead to flare-ups when the drug is interrupted. However, 56 Ghanaian participants with documented hepatitis B infection showed no changes in liver function tests after drug cessation.

The CDC is sponsoring two ongoing efficacy trials of PrEP. A study among injection drug users in Thailand is evaluating tenofovir alone, while a Botswanan study is looking at Truvada. A new, NIH-sponsored efficacy trial of Truvada as PrEP in high-risk gay men in Peru and Ecuador has just cleared its final regulatory hurdle in Peru, and enrollment should have begun by the time this report is published. The trial was initially slated to enroll 1,400 participants but will likely be expanded to 3,000 in order to bolster the statistical power and ensure that the efficacy results can be clearly interpreted.

Microbicides

Microbicides are substances that aim to prevent HIV infection (and possibly other sexually transmitted infections) via topical application to the vaginal or rectal surface prior to sex. One major advantage to such interventions, if they were to work as intended, is that they could potentially be used by women who may not be able to control whether or not their partners use condoms. However, paralleling some of the debates that have occurred in the HIV vaccine field, there has been controversy regarding the potential effectiveness of the current lead microbicide compounds and the process by which candidates are selected for efficacy trials.

In 2007, microbicide researchers experienced a setback when two efficacy trials of a candidate called Ushercell (an adsorption inhibitor) needed to be stopped because the active product arms had higher HIV infection rates than the placebo arms. The imbalance reportedly only was seen at some of the study sites in one of the trials, but both were

stopped as a safety measure. An investigation into the trial outcome is ongoing. Meanwhile, a microbicide efficacy trial of the surfactant compound Savvy was terminated in September 2006 after a DSMB review found no evidence of any protective effect.

Ideal Elements of a Microbicide

The four guiding principles of microbicide design are "cheap," "safe," "effective," and "acceptable." Furthermore, it would be highly advantageous if someone could use a microbicide without detection by the sexual partner. A rectal product is also desirable, but no candidates are yet in human trials. The microbicide field therefore faces the challenge of not only finding compounds, but of developing user-friendly delivery methods (a science in itself). A key long-term goal is the development of formulations or devices (such as intravaginal rings) to facilitate the slow release of the microbicide over a period of days or months.

Adsorption Inhibitors block the binding of HIV to target cells. Two absorption inhibitors are being assessed as microbicides in phase III efficacy trials: **carageenan (Carraguard)** and **PRO 2000**. Results from these trials are anticipated in late 2007 and 2008/2009, respectively. A small macaque study demonstrated protection against SHIV89.6PD infection in four of eight animals treated with PRO 2000, but there are no published challenge experiments using Carraguard. The Ushercell trial outcome led to additional DSMB reviews of the ongoing trials of adsorption inhibitors, but no evidence of safety concerns has emerged.

Acid-Buffering Agents. A key aspect of vaginal health is the maintenance of a low pH by hydrogen peroxide-producing lactobacilli. Several microbicides are designed to maintain the acidity of the vagina, thereby making it inhospitable to viruses like HIV. One such agent, **BufferGel**, is being studied in a phase IIb efficacy trial with PRO 2000.

Antiretrovirals. A number of microbicides that have more direct antiretroviral effects, including several reverse transcriptase inhibitors, are in early-phase human trials. A gel form of the drug tenofovir is current-

ly entering a phase IIb trial in South Africa. The reverse transcriptase inhibitor UC-781, originally developed by Uniroyal, is in a phase I trial sponsored by BioSyn. The International Partnership for Microbicides (IPM) is developing a non-nucleoside reverse transcriptase inhibitor, dapirivine gel (licensed from Tibotec and formerly known as TMC120); the organization hopes to move it forward into a phase III trial involving 10,000 women within the next few years. Following on the heels of these compounds are preclinical candidates that target attachment and entry of HIV; IPM has licensed the CCR5 inhibitor CMPD 167 from Merck and the attachment inhibitor BMS-378806 from Bristol-Myers Squibb.

Immune-Based Therapies

Immune-based therapies (IBTs) comprise a broad and somewhat fuzzy category of treatments that aim to exert therapeutic effects by acting on the human immune system. IBTs can be loosely subdivided into therapies that try to boost the immune response to HIV itself (e.g., therapeutic vaccines), those that may improve immune function and/or clinical health overall (e.g., cytokines like IL-2 and IL-7 and anti-inflammatory approaches), and futuristic gene therapies that may alter the make-up of the immune system in ways that ameliorate the harmful effects of HIV.

The development of IBTs has been hampered by the lack of a clear pathway toward approval. The large IL-2 trials mentioned in the introduction (ESPRIT and SILCAAT) were initiated in an attempt to determine whether the addition of the cytokine to ART would be clinically beneficial in a large population of people with HIV (a necessary requirement for the manufacturer to seek FDA approval). However, the effectiveness of ART has so dramatically reduced the number of clinical events that these trials have been forced to continue beyond the originally planned five years; it is unclear if they will ever be able to achieve their goals.

The problems associated with IBT development suggest that IBTs should be targeted toward needs that remain unmet in the era of effective ART. Recent data suggest that individuals who experience poor CD4 T-cell reconstitution on treatment may be at an increased risk for clinical events that traditionally have not been considered HIV-related, such as liver and kidney disease, cardiovascular problems, and cancers not previously classified as opportunistic. Similar findings emerged after the early termination of the Strategies for the Management of Antiretroviral Therapy (SMART) trial, which found that interrupting ART was associated with an increased risk of cardiac and liver problems that heretofore were widely assumed to represent drug toxicities. Future efficacy trials of IBTs potentially could be designed to include these non-traditional endpoints.

In addition to improving immune reconstitution and clinical health of people who remain immune suppressed despite ART, there are a number of other conceivable goals for IBTs:

- Elimination of the need for ART by replacing ART or inducing post-ART remission/cure;
- Delaying the initiation of ART;
- Allowing safe intermittent use of ART;
- Supplementing the anti-HIV effects of ART (allowing ART to work for longer and/or enhancing the anti-HIV effects of ART);
- Maintaining immune function in people for whom ART is failing; and
- Targeting drug-resistant HIV in people with multidrug resistance.

Each scenario presents its own challenges in terms of designing efficacy trials that could lead to licensure. As the IBT pipeline currently stands, however, few products are close to this stage of development.

Beyond the potential uses listed above, the desired characteristics of an IBT would be much the same as other therapies: broadly effective, safe, cheap, and convenient.

HIV Therapeutic Vaccines Pipeline 2007

Therapeutic HIV Vaccines in Clinical Trials

Phase II

ALVAC vCP1452: Canarypox—*Aventis Pasteur*

Gag, Nef, Pol lipopeptides: Peptides—*ANRS; Aventis*

CD4-specific T-Cell Vaccine: Autologous T cells—*Soroka Medical Center, Israel*

DCV-2: Autologous dendritic cells—*Hospital Clinic of Barcelona*

AGS-004: Autologous dendritic cells—*Argyros Therapeutics; ACTG*

LC002 (DermaVir): DNA—*Research Institute for Genetic & Human Therapy*

Data generated by studies of long-term non-progressors have played a key role in guiding the development of therapies aimed at bolstering the immune response to HIV. As outlined in the box on T-cell immunogenicity, recent studies have found that CD4 and CD8 T cells capable of performing multiple functions have advantages over those with more limited ability, such as the production of interferon gamma alone. It must be stressed that no proof exists that these types of T-cell responses are responsible for controlling HIV replication; they may emerge as a consequence of low viral load or they may work alongside other—as yet unknown—factors. For developers of therapeutic vaccines, however, these immunological parameters at least provide some guidance as to the types of immune response their constructs should induce.

In 2007, three new therapeutic vaccine candidates advanced into trials. Two strategies—one developed by researchers in Barcelona and the other by Jeff Jacobson and Agyros Therapeutics in the US—involve using an individual's own virus as a therapeutic vaccine. Both approaches also use dendritic cells cultured outside the body and mixed with the individual's HIV as the immunization vehicle. The Agyros approach uses viral RNA isolated from study participants, while the Barcelona researchers are inactivating the autologous virus

through heating. The third approach, developed by an Israeli research team led by Zvi Bentwich, is more unusual. The aim is not to enhance HIV-specific immunity but rather switch off a potentially harmful T-cell response against the CD4 molecule. Bentwich and colleagues have found that a substantial number of HIV-infected individuals display proliferative responses against CD4, suggesting a harmful autoimmune response. Their "T cell vaccination" strategy therefore uses these CD4-specific T cells as an immunogen in the hope that the immune system will respond by eliminating the autoreactive T cells. After one small study found that the approach was safe and may increase CD4 T-cell counts, a larger trial has begun recruiting.

Cytokine, Immunomodulator, and Gene Therapy Pipeline 2007

Cytokines, Immunomodulators, and Gene Therapies in Clinical Trials

Phase II	Phase III

Interleukin-2 (Proleukin, IL-2): Cytokine—*Novartis*

Human growth hormone (Serostim, HGHr): Growth hormone—*Serono*

Cyclosporine A: Immunosuppressive—*ACTG; AIEDRP*

VRX496: Ex vivo gene transfer—*VIRxSYS*

OZ1: Gene therapy—*J&J*

HGTV43: Ex vivo gene transfer—*Enzo Biochem*

Palifermin (keratinocyte growth factor): Growth factor—*Amgen*

One of the more surprising proposed IBTs is human growth hormone (HGH, Serostim), which is better known as an approved treatment for AIDS wasting syndrome. Several years ago, studies in mice indicated that HGH increased the size of the thymus. As a result, researchers became interested in the potential for HGH to speed naïve T-cell reconstitution in people with HIV. Mike McCune's research group at the Gladstone Institute measured thymus size and naïve T-cell counts in five individuals who were receiving HGH as a treatment for wasting. They found that thymic mass did indeed increase, and that this was associated with a rebound in naïve T-cell numbers. Two larger randomized studies have now been completed, a 20-person trial and a 60-person trial undertaken by the AIDS Clinical Trial Group (ACTG). Both studies reported increases in naïve CD4 T cells in people receiving HGH, but treatment was accompanied by the side effects typically associated with this product (arthralgias and myalgias, diaphoresis, fatigue, insomnia, carpal tunnel syndrome symptoms, edema, transaminitis, hyperglycemia, hyperamylasemia). The results of these trials suggest that HGH could potentially be evaluated for clinical benefit in individuals with incomplete immune reconstitution on ART, but safety is clearly a concern.

CD4 Reinfusion and Gene Therapies. A disparate collection of approaches involves infusing CD4 T cells (or in some cases CD34 stem cells) that are isolated from HIV-infected individuals, expanded, in some cases genetically modified in the laboratory, and then reinfused as potential IBTs. 2006 saw the publication of the results from a small phase I study of one such approach, dubbed VRX496. Five antiretroviral-experienced individuals received infusions of their own CD4 T cells modified with VRX496, an HIV-based vector that encodes an "antisense" gene designed to inhibit the HIV envelope gene. The treatment was well tolerated, viral loads remained stable (with one participant experiencing a significant decline) and CD4 T-cell counts remained above baseline in 4 of 5 participants after 1 year of follow up. Encouragingly, the vector also appeared to persist out to one year, remaining detectable in 0.02-0.04% of peripheral blood mononuclear cells. The researchers are now embarking on a phase II trial in collaboration with the manufacturer of VRX496, VirxSys.

One candidate—Johnson & Johnson's gene therapy, now dubbed OZ1—has advanced into a 74-person phase II efficacy trial. OZ1 contains genetic information which, once inside cells, encodes an enzyme known as a ribozyme, which chops up HIV's tat gene like a pair of scissors, thereby crippling the virus. OZ1 is introduced by harvesting stem cells from an individual, modifying them with the OZ1 gene, and then reinfusing them. Enrollment in the phase II OZ1 study was completed in February 2006. The study will assess the effect of OZ1 therapy on viral load and CD4 T-cell counts after two interruptions of antiretroviral therapy (of four and eight weeks duration, respectively).

Palifermin (recombinant human keratinocyte growth factor). Palifermin, manufactured by Amgen, is a recombinant form of a naturally occurring human protein, keratinocyte growth factor (KGF). Palifermin is licensed by the FDA to reduce the incidence of severe mucositis in people receiving cancer chemotherapies. The ACTG is conducting a trial that will evaluate whether palifermin can help restore CD4 T-cell counts in individuals with a discordant response to ART (controlled viral load but an inadequate rise in peripheral blood CD4 T-cells). A recent study in macaques undergoing transplantation

found that KGF significantly increased naïve T-cell counts and improved the immune response to new immunizations.

IL-7 is a cytokine which plays a key role in T-cell development and naïve and memory T-cell proliferation and survival. Results from two phase I trials of IL-7 in people with HIV reported substantial increases in CD4 and CD8 T-cell counts even at the lowest dose studied. The drug was well tolerated. These results suggest that IL-7 may be an appropriate candidate for studies in people with inadequate immune reconstitution despite ART.

ISBN 978-0-9791073-2-0