What's in the Pipeline:
New HIV Drugs, Vaccines, Microbicides, HCV and TB Therapies in Clinical Trials

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About TAG. The Treatment Action Group (TAG) fights to find a cure for AIDS and to ensure that all people living with HIV receive the necessary treatment, care, and information they need to save their lives. TAG focuses on the AIDS research effort, both public and private, the drug development process, and health care delivery systems. We meet with researchers, pharmaceutical companies, and government officials to encourage exploration of understudied areas in AIDS research and speed up drug development, approval, and access. We work with the World Health Organization and community organizations globally, and strive to develop the scientific and political expertise needed to transform policy. TAG is committed to working for and with all communities affected by HIV.

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Foreword
by Mark Harrington

Twenty-five years into the global HIV pandemic, 40 million people are living with the virus and some 25 million have died. According to UNAIDS, five million people were newly infected last year and 3.1 million died. By the end of 2005, according to the World Health Organization, about 1.3 million HIV-infected persons in developing countries were receiving antiretroviral therapy (ART)—a fourfold increase in just two years, with the most dramatic increase (800%) in sub-Saharan Africa. However, WHO recognizes that roughly 6.5 million people are in danger of dying from HIV/AIDS in the next two years, which means some 5 million in desperate need of ART are still unable to access it. A recent letter in *The Lancet* suggests that far more may currently need treatment; "Applying the WHO guidelines would then give…a total of 11.7 million who should be eligible." (England 2006)

If current guidelines on when to start ART are revised to recommend ART initiation at higher CD4 levels, then the number of people who need ART will increase further.

ART is working very well where it is available. A recent international collaboration compared 18 ART programs in Africa, Asia, and South America with 12 HIV studies from Europe and North America by looking at first-year mortality among 4,810 and 22,217 persons starting ART in the two settings. While complete follow-up data were available on all patients from Europe/North America, just 57% (2,725) of "patients from low-income settings were actively followed up and included in survival analyses." Results were encouraging, though patients initiating therapy in low-income settings were sicker, had lower baseline CD4 cell counts and higher early mortality:

> Compared with high-income countries, patients starting HAART in low-income settings had lower CD4 cell counts … were more likely to be female … and more likely to start treatment with a non-nucleoside reverse transcriptase inhibitor (NNRTI). At 6 months, the median number of CD4 cells gained…and the percentage of patients reaching HIV-1 RNA levels below 500 copies/mL…were similar. [Note: In many low-income countries viral load is not available.] Mortality was higher in low-income settings than in high-income settings. The adjusted hazard ratio (HR) of mortality comparing low-income with high-income settings fell from 4.3 (95% CI 1.6-11.8) during the first month to 1.5 (CI 0.7-3.0) during months seven through twelve. The provision of treatment free of charge in low-income settings was associated with 77% lower mortality (adjusted HR 0.23, 95% CI 0.08-0.61). (ART-LINC and ART-CC 2006)

A recent modeling exercise calculated the survival benefits of AIDS treatment (PCP and MAC prophylaxis, increasingly potent and tolerable ART, and prevention of mother-to-child transmission). The authors concluded that:

> Treatment for patients with AIDS in care in the United States since 1989 yielded a total survival benefit of 2.8 million years. [Prevention of mother-to-child transmission] averted nearly 2,900 infant infections, equivalent to 137,000 additional years of survival benefit…At least 3.0 million years of life have been saved in the United States as a direct result of care of patients with AIDS. (Walensky 2006)

Research and activism have been the twin engines driving progress against the pandemic. Politics, prejudice, and scientific hurdles remain the three chief obstacles to its control. The response to HIV/AIDS around the world has been dramatically transformed since 1996, when highly active antiretroviral therapy arrived. Death rates in developed countries from HIV/AIDS have declined by two-thirds. Since the Durban AIDS conference in 2000, the advent of cheap generic antiretroviral combinations in 2001, the formation of the Global Fund to Fight AIDS, TB and Malaria (GFTAM) in 2002, the establishment of the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) in 2003, and the WHO

'3x5' initiative and subsequent efforts at global scale up, world leaders have grudgingly come to declare a commitment to:

> Pursue all necessary efforts to scale up nationally driven, sustainable and comprehensive responses to achieve broad multisectorial coverage for prevention, treatment, care and support, with full and active participation of people living with HIV, vulnerable groups, most affected communities, civil society and the private sector, towards the goal of universal access to comprehensive prevention programs, treatment, care and support by 2010. (UN General Assembly 2006)

According to UNAIDS, annual resources for scale-up towards universal access must triple by 2008 to $20-23 billion per year, yet the Global Fund lacks committed resources beyond the current round six. In Moscow last month, G8 leaders tepidly reaffirmed their commitment to Universal Access, as well as to The Global Plan to Stop TB and to expanded efforts to control malaria, avian influenza, and other emerging epidemics. Just how these commitments will be realized remains unclear (G8 2006).

In the first ten years of AIDS drug development, the FDA approved seven drugs: five nucleoside analogue reverse transcriptase inhibitors (AZT, ddI, ddC, d4T, 3TC) and one protease inhibitor, Roche's saquinavir. Since the beginning of 1996, the FDA has approved three non-nucleoside reverse transcriptase inhibitors (nevirapine, delavirdine, efavirenz), three new nucleotide or nucleoside analogues (abacavir, tenofovir, 3TC), ten protease inhibitors (ritonavir, indinavir, nelfinavir, saquinavir soft gel capsules-

FDA Antitretroviral Approval Dates				
Drug	Brand name	Sponsor	Approval date	Class
AZT (zidovudine)	Retrovir	Burroughs-Wellcome (now GlaxoSmithKline)	19 Mar 1987	NRTI
ddI (didanosine)	Videx	Bristol-Myers (now Bristol-Myers Squibb)	9 Oct 1991	NRTI
ddC (zalcitabine)*	HIVID*	Hoffmann-LaRoche	19 Jun 1992	NRTI
d4T (stavudine)	Zerit	Bristol-Myers Squibb (BMS)	24 Jun 1994	NRTI
3TC (lamivudine)	Epivir	GlaxoSmithKline (GSK)	17 Nov 1995	NRTI
saquinavir (SQV)	Invirase	Hoffmann-LaRoche	6 Dec 1995	PI
ritonavir (RTV)	Norvir	Abbott	1 Mar 1996	PI
indinavir (IDV)	Crixivan	Merck	13 Mar 1996	PI
nevirapine	Viramune	Boehrigner Ingelheim	21 Jun 1996	NNRTI
nelfinavir (NFV)	Viracept	Agouron (now Pfizer)	14 Mar 1997	PI
delavirdine (DLV)	Rescriptor	Pharmacia & Upjohn (now Pfizer)	4 Apr 1997	NNRTI
AZT/3TC	Combivir	GSK	27 Sep 1997	NNRTI
saqunavir sgc*	Fortovase*	Hoffmann-LaRoche	7 Nov 1997	PI
efavirenz (EFV)	Sustiva	DuPont (now BMS)	17 Sep 1998	NNRTI
abacavir (ABC)	Ziagen	GSK	17 Dec 1998	NRTI
amprenavir	Agenerase	GSK	15 Apr 1999	PI
lopinavir (LPV)/ritonavir	Kaletra	Abbott	15 Sep 2000	PI
ddI enteric coated	Videx EC	BMS	31 Oct 2000	NRTI
AZT/3TC/ABC	Trizivir	GSK	14 Nov 2000	NRTI
tenofovir DF (TDF)	Viread	Gilead	26 Oct 2001	NRTI
enfuvirtide (T-20)	Fuzeon	Hoffmann-LaRoche / Trimeris	13 Mar 2003	EI
atazanavir	Reyataz	BMS	20 Jun 2003	PI
FTC (emtricitabine)	Emtriva	Gilead	2 Jul 2003	NRTI
ABC/3TC	Epzicom	GSK	2 Aug 2003	NRTI
FTC/tenofovir DF	Truvada	Gilead	2 Aug 2003	NRTI
fosapmrenavir	Lexiva	GSK	20 Oct 2003	PI
tipranavir	Aptivus	Boehringer Ingelheim	22 Jun 2005	PI
darunavir	Prezista	Johnson & Johnson/Tibotec	23 Jun 2006	PI
TDF/3TC/efavirenz	Atripla	Gilead/BMS [Gilead/Merck in much of world]	12 Jul 2006	2 NRTI/1 NNRTI

soft gel cap saqunavir (Fortovase) and zalcitabine (HIVID) were discontinued by Roche on 15 February 2006.

now withdrawn, amprenavir, lopinavir/r, atazanavir, fosamprenavir, tipranavir, and darunavir) and one entry/fusion inhibitor (T-20) (see table). FDA has also approved an increasing number of two- and three-drug fixed-dose combinations such as Combivir (AZT/3TC), Trizivir (AZT/3TC/ABC), Epzicom (ABC/3TC), Truvada (3TC/TDF) and recently, Atripla, a once-daily triple combination of 3TC/TDF/efavirenz. FDA has also approved a number of generic FDC products for sale internationally but not in the U.S. Unfortunately progress in treatment research over the past twenty years has not been matched by progress in establishing safe and effective preventive interventions such as microbicides, pre-exposure prophylaxis (PrEP) or vaccines.

TAG's *2006 Pipeline Report* focuses on a key part of the product development pipeline for biomedical interventions to prevent or treat HIV and its two most common deadly global co-infections: tuberculosis (TB) and hepatitis C virus (HCV) infection.

So what's in the pipeline?

Rob Camp's chapter reveals that the ARV pipeline is robust, with at least 20 new compounds in pre-approval clinical trials and three entering the final stages. These include four NRTIs, three directed against common HIV strains resistant to 3TC or FTC due to the M184V mutation, and one that has a putatively new mechanism of activity leading to 'catastrophic mutagenesis' of HIV. One NNRTI, Tibotec/J&J's etravirine (formerly TMC125) is in phase III trials and likely to be approved in the next year. Tibotec also has a backup compound in phase II. Boehringer Ingelheim's NNRTI BILR 355 is further behind in phase Ib/II. Protease inhibitor development seems to be slowing, with GSK's brecanavir (formerly 640385) slowly progressing through phase II and just one other PI entering phase I.

Entry inhibitors are moving forward at uneven rates. Pfizer's CCR5 inhibitor Maraviroc is in phase III and likely to be approved in the first quarter of 2007 provided that it proves effective and no safety problems emerge. Schering's CCR5 inhibitor has been plagued by problems with potency, pharmacokinetics and a disturbingly high rate of cancer. An array of other approaches including monoclonal antibodies from Human Genome Sciences, Progenics, and Tanox/Biogen are moving more slowly, as is BMS' gp120 blocker BMS-378806, Takeda's TAK-652 and Anormed's seemingly paralyzed AMD-070 CXCR4 antagonist. Other mechanisms under study include three integrase inhibitors from Merck, Gilead, and GSK/Shionogi, Panacos' maturation inhibitor bevirimat (formerly PA-457), a TAT-inhibiting monoclonal antibody from BioInvent, and the epilepsy/psychiatric agent valproic acid, of interest for expressing latently HIV infected cells.

The discovery and development of HIV integrase inhibitors illustrates the results that a focused, research-driven pharmaceutical company can accomplish at its best. The biggest news on the ARV front this year however came not from a new or approved drug, but rather from the largest randomized, controlled HIV treatment strategy trial ever conducted (the SMART study), whose results were presented at the 13th Conference on Retroviruses and Opportunistic Infections (CROI) in February 2006. SMART compared the risk and benefit of a virological suppression (VS) strategy using continuous ART to a drug conservation (DC) strategy, stopping ART when CD4 counts rose over 350 cells/mm^3 and restarting when CD4 counts dropped below 250. After just 14 months of average follow-up, 164 primary events occurred and the Data and Safety Monitoring Board recommended that the study terminate. All comparisons favored the VS arm; the relative risk of progression to a primary endpoint was 2.6 (118 events in DC vs. 46 in VS, p<0.0001). When adjusted for last known CD4 and viral load, the elevated risk was still 1.4. Perhaps the most surprising results were that pre-ART nadir CD4 did not predict progression and that the serious cardiovascular, hepatic, and renal events—which were projected to occur at greatest frequency in the VS arm due to drug-related toxicities—were more common in the DC arm, raising the possibility that some serious side effects previously attributed to ART may be due instead to underlying HIV disease.

SMART did not directly address the question of the best time to initiate antiretroviral therapy, but it showed that—for people already on ART—the CD4-guided structured treatment interruption strategy was inferior if therapy was stopped at 350 CD4 cells/mm^3 and restarted at 250. These results were reinforced in a West African setting by the ANRS 1269 Trivacan study that used the same CD4 starting and stopping thresholds in one of its three arms and ultimately terminated its CD4-guided STI arm in October 2005 (Daniel 2006).

TAG recently co-organized an international workshop, in conjunction with the National Institutes of Health (NIH) Office of AIDS Research (OAR), to develop scientific consensus on future directions in STI research, including the implications for when to start ART. There was a surprising consensus that, despite previous difficulties in carrying out when-to-start studies, there may be sufficient equipoise in the current moment—with global antiretroviral scale-up taking place amidst a backdrop of increasing uncertainty about both the number of people already needing ART (England 2006) and the optimal time to initiate it—to consider a randomized, controlled global when-to-start trial. In addition, the workshop highlighted outstanding research questions for which the use of carefully controlled STI or intermittent therapy is warranted (OAR 2006, forthcoming).

Progress in HIV drug development has not been matched by progress with immune-based therapies for HIV chemoprophylaxis, treatment, or prevention using microbicides or preventive vaccines. Richard Jefferys provides a sobering tour d'horizon of these enormous research fronts in the HIV research effort. He discusses the lack of seismic shifts and the continuing lack of a precedent for efficacy in these arenas. Results of two small studies using therapeutic vaccination during STI suggest that this strategy remains possible. On the preventive vaccine front, two approaches, both using adenovirus vectors with HIV proteins added, are likely to go into phase III over the next year. One hails from Merck and the other from NIH's Vaccine Research Center (VRC). These studies are likely to provide useful comparative and complementary information as the Merck approach does not include HIV-1 *env* gene sequences, while the VRC candidate does. HIV microbicides are moving into phase III, which is encouraging, although the preclinical basis for choosing microbicide approaches is not particularly robust. Pre-exposure prophylaxis (PrEP) research, which has been dogged by ethical, political, and logistical concerns, remains on a slow track, though there are encouraging new primate data on two-drug pre-exposure prophylaxis using tenofovir DF and 3TC.

The past year has seen significant development of long-term financing commitments and collaborative research infrastructure for HIV vaccine development, with the NIH establishment of a giant Center for HIV/AIDS Vaccine Immunology (CHAVI) one year ago and the Bill & Melinda Gates Foundation award of $287 million over five years to sixteen groups to coordinate and increase HIV vaccine research efforts. CHAVI funding could amount to $300 million over seven years.

More sobering is the shrinking of public investment in biomedical research in the United States, where we have seen two years of stable, followed by declining, new funding overall for the National Institutes of Health (NIH) as well as at the Centers for Disease Control and Prevention (CDC). If NIH and CDC do not soon begin to receive budget increases, the long-term prospect for biomedical research—including the basic science research that yields breakthroughs against diseases such as HIV, HCV, and TB—will bleaken.

Tracy Swan's hepatitis C report shows that while research is moving forward on a variety of fronts to treat HCV, an infection affecting 127 million people worldwide and at least four million in the U.S., efforts remain underfunded, uncoordinated, and relatively unfriendly to oversight or the involvement of activists from affected communities. Swan discusses the three HCV protease inhibitors in development and reviews preliminary data on four HCV polymerase inhibitors, one alpha-glucosidase inhibitor, and a host of immune-based approaches.

According to Swan, "the [current] hepatitis C treatment scenario resembles pre-HAART era HIV: a sub-optimal standard of care, with a pipeline full of promising agents." Swan recommends increased funding for treatment strategy trials that use new and approved anti-HCV agents in combination to optimize the standard of care, standardization of assays, longer-term follow-up in clinical trials, the establishment of correlates of immunity for preventive HCV vaccines; assay development for HCV drug resistance, and studies in high-risk and affected populations, including those living with HIV/HCV coinfection. Swan also calls for further refinement in study populations, investigation of HCV genotype-specific treatment strategies, and validation of non-invasive serum biomarkers to replace biopsy, the gold standard for prognosis and treatment response.

Swan suggests regularly updated HCV treatment guidelines, which could improve uptake and use of HCV treatment, and better care and treatment programs for those living with HCV infection. Finally, she notes, "the hepatitis C universe is a sparsely populated frontier for treatment activism. The notion of an HCV community is unfamiliar to companies developing HCV therapies. Few companies have met with community members and some have been reluctant to share even minimal information...This lack of transparency and communication is retrograde and unproductive." Here Swan reinforces Rob Camp's earlier call for greater transparency on the part of clinical trial sponsors—both public and private—about clinical trials around the world.

Disease caused by *Mycobacterium tuberculosis* (MTB) has been with humans for one million years, yet it still infects one third of the human race, kills two million people a year, and is the leading killer of people with HIV. The problem with TB is that its vaccine does not prevent pulmonary disease, its diagnosis is difficult or impossible in resource-limited settings with high HIV prevalence, and its treatment—while curative—requires six months of burdensome combination therapy, often directly-observed. Furthermore, drug interactions remain a concern between the most common TB and anti-HIV drugs. After forty years without a single new drug class being discovered for TB, the past five years have seen a revival of research interest.

Javid Syed provides an overview of six TB drugs currently in the clinic and five potential vaccines and immunotherapies. Progress since last year has been slow, with two drugs (the already-approved fluoro-quinolones gatifloxacin and moxiflocacin) now in phase II/III studies, two new classes (J&J's diarylquinoline TMC207 and Otsuka's nitroimidazopyran OPC-67683) in early bactericidal activity phase II studies, and two other new classes (the Global Alliance's nitroimidazopyran PA-824, and Lupin's pyr-role Sudoterb (LL-3858) in early phase I research. Publicly funded infrastructure for TB clinical trials through the CDC funded TB Trials Consortium (TBTC) is shrinking by 10% per year just as these new drugs come on board. The Gates Foundation recently awarded the Global Alliance for TB Drug Development (GATDD) $104 million to expand its research over the coming years, but GATDD has yet to establish the clinical trials infrastructure necessary for successful research.

NIH funding for TB research was just $157 million in 2005. The Gates Foundation, the second biggest funder, announced a TB drug discovery accelerator grant program in 2006 that will award $40 million for two years to study twelve top questions in TB preclinical drug development. Nonetheless, without greater public sector investment, TB drug discovery and development will be far slower than necessary.

Researchers still lack a clear consensus on why the BCG TB vaccine, available since the 1920s and given to 100 million children each year, fails to protect against pulmonary disease in older children, adolescents, and adults. The Gates-funded Aeras Global TB Vaccine Foundation is investigating a number of new vaccine approaches in conjunction with academic and industry partners including Corixa, Crucell, GSK Bio, the Max Planck Institute, Oxford, Statens Serum Institute, and UCLA. Aeras is looking at improved recombinant BCG approaches as well as trying to define a BCG prime/protein subunit or viral

vector boost approach to move forward into efficacy trials. Because BCG is currently given just after birth, and boosting with BCG is ineffective, it is unclear how large and long these TB vaccine trials are likely to be, but they will ultimately take decades. Meanwhile a group from Dartmouth and SR Pharma in the UK continues to study a heat-inactivated *Mycobacterium vaccae* as a potential immunotherapy for people with multidrug-resistant (MDR) TB, despite conflicting and inconclusive data from a decade of previous research.

As Syed notes, the world must at least triple its investment in TB research and development, as well as in scaling up worldwide control of TB-including TB/HIV and MDR-TB-if we are to achieve the goals laid out in *The Global Plan to Stop TB: 2006-2015* (WHO/Stop TB 2006). Syed concludes that research progress against HIV/AIDS in the past twenty years—particularly in terms of treatment research—has benefited from focused community advocacy, which created political will, helped to mobilize scientific resources, drew in public and private sector investment and resulted in a healthy drug development pipeline. By contrast, the low annual funding for TB research is a measure of insufficient political will with respect to TB.

His prescription includes strengthening TB awareness and advocacy, increased transparency and tracking of TB funding, and advocacy to persuade political, public health and scientific leaders to intensify public sector investment in TB research. As Syed concludes, strong public-sector support includes funding basic and operational research to ensure that the TB pipeline is robust and accessible to people in greatest need. Equally crucial are strategies which can support the goals for TB control and elimination in ways that also address some of the related social justice inequities at the core of TB. Increased collaboration among these constituencies can strike at the heart of inequalities such as poverty, stigma, and marginalization that structure people's access to health care and often preclude the involvement of those who are most likely to die from TB—people who have the most to gain from TB control—in the struggle to eliminate TB.

Clearly, this report carries a message which applies to the overall fields of HIV, HCV, and TB prevention and treatment research. Increased investment in basic, applied, clinical, and operational research, greater mobilization of public sector resources to support research, prevention, care, and treatment, and, crucially, the involvement of educated and mobilized activist communities of people living with and affected by these global killer diseases are each required if we are to conquer these diseases in the coming quarter-century.

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Antiretroviral Pipeline 2006
by Rob Camp

Introduction

Combination antiretroviral therapy does not cure infection with HIV, but the progressive introduction of new drugs and classes, simplified treatment regimens, and reduced toxicity and adherence burdens have led to sustained declines in rates of HIV-related morbidity and mortality wherever ART is available. Nonetheless, because so many people experience treatment failure, whether due to drug resistance, tolerability or toxicity, new drugs and drug classes are urgently needed.

The most recent U.S. guidelines on antiretroviral treatment include fifteen pages of tables on adverse effects and how to manage them. Some are potentially life threatening, others chronic, cumulative, over-lapping, and sometimes irreversible (DHHS 2006). While some current drugs are relatively benign, few combination regimens are wholly non-toxic. The guidelines also newly recommend resistance testing for ARV-naïve patients to detect cases of persons infected with resistant virus. The IAS-USA regularly publish-es updated lists of ARV drug resistance mutations. The latest edition spans seven pages (IAS-USA 2005).

With over 40,000 new HIV infections annually in the U.S. and over 5.1 million globally, the need for better drugs will continue to grow. According to UNAIDS, global spending on HIV/AIDS must at least triple to $20-23 billion by 2008 to keep up the momentum, but sufficient new resources are not yet in view. Patent laws in some countries may also restrict access to some newer ARVs in resource-limited settings. Even in the U.S., efforts against HIV disease are sporadic with no clearly defined national plan for comprehensive, science-based prevention, treatment and support. Fifty percent of Americans who need ART are not in care, and some communities are devastated by HIV—particularly communities of color, men who have sex with men, injecting drug users, and the poor (Open Society Institute 2006). Women make up a significant part of those needing treatment in the U.S. and worldwide.

Twenty-three new anti-HIV drugs are now in clinical trials. None of these is likely to be a cure for AIDS. We may be moving toward fewer pills a day, but eradication of HIV remains a distant goal.

Landscape of Current Treatment

Current first-line ART is based on simultaneous initiation of three drugs: a recommended anchor non-nucleoside reverse transcriptase inhibitor (efavirenz) or protease inhibitor (lopinavir/ritonavir) combined with a backbone of two nucleoside analogue RTIs (once-daily tenofovir/FTC or twice-daily AZT/3TC). Second-line therapy is usually a complementary triple-drug regimen with a new nucleoside backbone, and often, another ritonavir-boosted protease inhibitor. For the growing number of individuals with triple class experience and class-wide resistance to at least two classes of oral ARVs, salvage therapy options including recently approved PIs such as tipranavir or darunavir—each boosted with ritonavir—may be used with subcutaneous injections of twice-daily enfuvirtide (T-20). Available treatment options for triple-class experienced individuals are suboptimal. In many resource-limited settings now undertak-ing ambitious ARV scale-up programs, second-line therapies are rare, with only limited global access to the new heat-stable formulation of lopinavir/ritonavir from Abbott (MSF 2006).

The community routinely recites to industry, FDA, and researchers the many gaps in information that accompany ARVs at the time of approval and persist far too long afterwards (Camp 2004):

- More data should be available on pharmacokinetics and pharmacodynamics of drugs in diverse populations, including: women, African Americans and other ethnic groups, people with hepatic or renal impairment, people coinfected with HBV, HCV or TB, and children.
- More drug-drug interaction studies should be completed at the time of approval, including studies that investigate interactions between ARVs and methadone, birth control hormones and TB drugs such as rifampin (rifampicin).
- Study populations must reflect the makeup of the epidemic by adequately representing

women and people of color. Clinical trial sponsors need to work with clinics capable of enrolling diverse groups of individuals more rapidly.

- After drugs have been approved, promises made by companies to conduct post-marketing research must not languish. Currently FDA has no effective means to compel companies to complete phase IV commitments. Congress should pass legislation to give FDA more authority in this area.
- Better systems are urgently needed to monitor chronic and long-term side effects of drugs post-approval. The current, voluntary, adverse events reporting system may miss substantial toxicity. A network of sentinel practices to report unusual symptoms could viably enhance the current inadequate *Med Watch* system. The need for a better system to detect and track side effects (such as the emergence of lipodystrophy syndrome after the approval of the protease inhibitors) has long been a concern for the community (Huff 2003).

These themes reflect questions that arise after approval of every drug, and too often persist for years: How should the drug be used and managed? Which HIV infected populations will benefit?

Desired Elements of Future Therapies

Ideally, future therapies need to be affordable, simple to adhere to, have few side effects and no cross-resistance. Of course, they must also be potent anti-HIV agents. First-line treatments are quite good in all these areas, but in heavily treatment experienced and salvage settings, the bar for approval is much lower; if the drug appears to offer some benefit, the risk/benefit ratio tilts somewhat away from safety. Risk/benefit needs to be more clearly defined in populations that will use the drug in the real world.

In the last couple of years, many sponsors have tried to develop new NRTIs, NNRTIs and PIs with resistance profiles likely to work against the most common emergent mutations. While this approach has worked for tipranavir/r and darunavir/r, it has yet to bear fruit for reverse transcriptase inhibitors. Table One includes three NRTIs purportedly active against virus with the M184V mutation associated with 3TC and FTC resistance. These drugs are all sponsored by small, inexperienced companies, and have stalled in phases I/II. The first new NNRTI since 1997, Tibotec's etravirine, is steadily moving towards approval. In the PI class, FDA licensed BI's Aptivus and J&J/Tibotec's Prezista within twelve months of each other. Both drugs are boosted with ritonavir; the first with a toxicity profile that borders on the gothic, and the second not yet studied adequately in all populations. The excessive price of Aptivus was a particular disappointment, one compounded by increasingly alarming safety and potency issues. The price of Prezista, while less than Aptivus, is still a daunting $25 per day. With ten protease inhibitors on the market, it's unclear what a new agent must offer in order to make it through the pipeline. Only two new PIs are in pre-approval clinical trials, and at least two companies have recently questioned the feasibility of taking the class forward.

New Drug Classes

HIV research is on the brink of ushering in a series of new antiretroviral drug classes that just may revolutionize the paradigms for how ART regimens are constructed. The first entry inhibitor (via T-20 injection) reached approval in 2002, and research is closing in on a second mechanism of inhibiting entry by blocking CCR5 coreceptors required by HIV to enter the cell. Pfizer's CCR5 antagonist maraviroc is in phase III, with FDA filing expected towards the end of 2006. Schering's vicriviroc—impeded by inadequate corporate investment and confusion on proper dosing—lags behind by some months. Six other entry inhibitors (including Anormed's CXCR4 antagonist AMD-070; BMS-378806, an oral gp120 blocker; Takeda's TAK-652 CCR5 inhibitor; Human Genome Sciences' CCR5-blocking monoclonal antibody HGS-004; the Progenics mAb PRO-140, and Tanox/Biogen's anti-CD4 mAb TNX-355) are all becalmed in phase I/II studies.

Although there are many major unknowns with entry inhibitors (the frequency and significance of tropism switching, use of assays to measure tropism, toxicities due to blocking host cell signaling, antiviral activity), what they potentially offer is freedom from cross-resistance to pre-existing classes.

Moving along swiftly is another breakthrough class of compounds, the integrase inhibitors, which block HIV DNA from integrating into the host cell's DNA. After ten years of arduous preclinical research defining the molecular mechanism, screening lead compounds, and turning them into drugs that could enter clinical testing, two agents are in phase II/III efficacy trials. Researchers at Merck & Co. deserve the most credit for bringing this difficult class forward.

Finally, maturation and budding, late steps in the viral life cycle, have an active antagonist or two emerging. Tat inhibitors are back over ten years after one from Roche crashed and burned. Still, more avant-garde approaches are being studied, such as using valproic acid (Depakote, an approved drug to treat epilepsy and bipolar disorder) to inhibit histone deacetylase 1 (HDAC1) and attempt to flush HIV-1 out of latently infected cells (Lehrman 2005; Routy J-P 2005; Gadd 2005).

Pipeline Review

Twenty-three new antiretroviral drugs are being tested in humans. The past year saw one new drug approved, darunavir/r, one drug retired due to lack of efficacy, Pfizer's NNRTI capravirine, a legacy of the Agouron purchase, and two drugs discontinued due to toxicity: Incyte's reverset (dexelvucitabine [DFC]) and GSK's CCR5 blocker aplaviroc (GSK 2005).

With the HIV market maturing, there are still many drugs in development both in existing classes (four NRTIs, three NNRTIs, two PIs) and new ones (eight entry inhibitors, three integrase inhibitors and three that exploit other mechanisms). However, we have several concerns.

One is that current funding at the National Institutes of Health (NIH) and elsewhere for basic investigator-initiated research is flat or falling. This will reduce the chances for breakthrough discoveries that could yield tomorrow's new drug candidates. A second concern is the continuing threat that industry will transfer resources away from HIV as it has from other infectious diseases. Here, too, the shrinking public investment pool may have a deleterious downstream effect.

A third concern is that newer, smaller companies such as Achillion, Ambrilia, Anormed, Avexa, BioInvent, Human Genome Sciences, Koronis, Panacos, Pharmasset, Progenics, Takeda, and Tanox lack industrial heft and drug development experience. Their compounds are moving forward slowly. Only nine drugs in the pipeline are from companies that have succeeded in getting an ARV drug approved. While we do not support further consolidation in the pharmaceutical industry, some of the smaller sponsors in the field need a boost of capital and experience from larger companies that have successfully brought ARVs to market. Indeed, Gilead has shown that it is possible to survive with a well thought-out pipeline even as a small company.

Another area of concern is that more and more drugs are relying on ritonavir boosting to achieve therapeutic levels in the blood by inhibiting the cytochrome P450 isoenzyme CYP3A4. All but one of the ten approved protease inhibitors benefit from ritonavir, the 3A4 inhibitor of choice. One of the two integrase inhibitors (Gilead's GS-9137) uses it, one of the first two CCR5 inhibitors (Schering's vicriviroc) needs it, and even an NNRTI in development (Boehringer Ingelheim's BILR 355) can't live without it. Given the near ubiquity of Norvir, its exorbitant price can't be ignored. We desperately need alternative candidates that inhibit the CYP3A4 pathway, such as a tall glass of pharmacologically well-characterized grapefruit juice (Row 2006).

Phase III

Phase III studies are key trials that determine if a new drug is worthy of being approved for marketing. In phase III trials, an investigational agent is given to large groups of people (500–1,000+) to evaluate its effectiveness, monitor side effects, compare it to an approved standard regimen, and collect information that will allow the drug to be used safely. Three drugs, currently in phase III trials, could be available in pharmacies by mid-2007—Pfizer's CCR5 blocker maraviroc, Tibotec/J&J's NNRTI etravirine (formerly TMC125) and Merck's integrase inhibitor, MK-0518. Two are from new classes.

Entry Inhibitors

Entry inhibition covers a broad range of targets including virus-host cell attachment, fusion, CD4 binding, and co-receptor binding to CCR5 and CXCR4. Mechanistically, these inhibitors target separate stages in the entry process and may be less likely to induce cross-resistance than currently available drugs, raising the possibility of complementary action to make an entry-inhibiting triple play.

There is still much to learn about these new compounds, including: the significance of shutting off coreceptors; defining the effect on HIV tropism switches (from the more common, less rapidly pathogenic R5 HIV to the more aggressive, destructive X4 strains); toxicities, and the need for boosting with ritonavir. Nevertheless, progress on a number of compounds that inhibit R5 HIV or block entry via other mechanisms may usher in potent new tools for inhibiting HIV.

Maraviroc (MVC) is a CCR5 antagonist currently in phase IIb/III trials sponsored by Pfizer. During the 2005 International AIDS Society (IAS) Conference, safety and efficacy data from six multiple dose studies were summarized (McHale 2005). Overall, 195 people, including 40 women, were dosed with maraviroc; two of six studies were in HIV-positive people. Ten-day maraviroc monotherapy, taken either as 300 mg daily or 300 mg twice daily, resulted in mean HIV RNA reductions of 1.60 and 1.84 $\log_{10}$, respectively. Two of 66 patients had emergent X4 virus; one reverted after maraviroc was stopped, the other persisted for several months with no effect. Maraviroc is a substrate for CYP3A4 and requires dose reduction when used with ritonavir. Five treatment-related drug discontinuations were reported, including three due to hypo tension, one to elevated transaminase levels and another to rash. Clinically significant increases in liver function tests (LFTs) occurred in seven people.

Late last year, after GSK announced aplaviroc's liver-related demise, Pfizer's maraviroc Data and Safety Monitoring Board (DSMB) reviewed phase II and III safety data through October 2005, and, not seeing further abnormal LFTs or related red flags, decided to move forward. Then, after two more cases of liver problems (November 2005 and January 2006), the DSMB strengthened the informed consent and again agreed to move forward. Nonetheless, the experience has further underscored the need for vigilant safety monitoring and analysis of safety data prior to licensure—particularly given the background health state of many salvage patients and the risk of toxicity associated with drugs such as tipranavir/r. An analysis of people taking both MVC and TPV/r showed no evidence of MVC-related hepatotoxicity (DSMB 2006; Abel 2006).

Pfizer has now completely enrolled four phase III trials of maraviroc; one in ARV-naïve people, two in experienced, and one in a population with mixed tropic (R5/X4) virus. The maraviroc phase III treatment-experienced trial is evaluating 150 mg twice daily plus optimized background therapy, compared to optimized background therapy alone. Participants have triple class experience or documented resistance to three ARV classes. Meanwhile, in January 2006, the DSMB met and reviewed pooled safety data and decided to stop the maraviroc 150 mg QD plus AZT/3TC arm of the naïve trial due to inferior performance vis-à-vis efavirenz plus AZT/3TC. The MVC 150 mg BID plus AZT/3TC arm continues in the naïve trial.

Old Classes, New Drugs

New drugs in existing classes are expected to offer benefits over existing drugs in terms of tolerability, ease of use, or treatment of resistant HIV strains.

NNRTI

Etravirine (formerly TMC125 from Tibotec/J&J) is the first NNRTI active against virus with mutations to existing NNRTIs such as efavirenz or nevirapine. Etravirine is now in phase III multinational registration trials with its partner of choice, darunavir/r, in the DUET trials (www.ClinicalTrials.gov NCT00254046/NCT00255099).

One study assessed baseline resistance parameters that influenced virological response. In the study, heavily pre-treated people with documented NNRTI resistance were randomized to either a standard of care control regimen or to one of two doses of etravirine plus an optimized background regimen (OBR). Ninety-four percent of participants had used an NNRTI. At baseline, people had a median of two NNRTI mutations. K103N was the most frequent mutation, followed by Y181C and G190A. Viral load reductions were 1.82 $\log_{10}$ 1.65 $\log_{10}$, 1.06 $\log_{10}$, and .66 $\log_{10}$ in people with no mutations, one mutation, two mutations, and three or four mutations, respectively. (Vingerhoets 2006).

A large phase III program of darunavir/r plus etravirine is underway in the DUET studies. In an earlier proof of concept trial to assess the feasability of this combination, investigators looked at the pharmacokinetics, safety, and efficacy of darunavir/r 600/100 mg BID and etravirine 200 mg BID (new formulation) plus NRTIs, with or without T-20. Resistance, safety, and efficacy were assessed. Ten of eleven subjects completed the study. Compared with historical controls, the pharmacokinetic results reflected unchanged exposure to darunavir and a greater than 30% reduced exposure to etravirine. At week six, all participants (all study subjects enrolled with two baseline NNRTI mutations) achieved at least a 2.0 $\log_{10}$ decrease in viral load with a median of -2.55 $\log_{10}$; 5/10 and 8/10 persons had viral load <40 and <400 copies/mL, respectively (Boffito 2006). The larger DUET studies enrolled over 1,000 people with HIV RNA levels over 5,000 copies/mL, NNRTI experience or resistance, and three or more primary PI mutations.

Integrase Inhibitors

MK-0518 is the first inhibitor of integrase-the step in HIV's lifecycle where the HIV genome is inserted into the host's DNA—to reach phase II/III efficacy trials. Two integrase inhibitors are now in the clinic, and several preclinical integrase programs are underway in drug discovery programs around the world (see TAG's preclinical ARV pipeline chart at www.aidsinfonyc.org/tag/tx/pipeline2006a.html).

Merck's research on HIV integrase inhibitors began in the early 1990s (LaFemina 1991). They developed binding assays, targeted integrase inhibition screening assays, and moved slowly and methodically through the process of screening compounds that could be developed into candidate drugs (Hazuda 1997)—an impressive illustration of what the pharmaceutical industry is capable of when it pursues innovative breakthrough science rather than me-too marketing schemes and made-up lifestyle drugs. They eventually concentrated on diketo acid strand transfer inhibitors and have defined the current state-of-the-art mechanism of action. The integrase inhibitor furthest along in clinical trials is Merck's MK-0518.

Interim results from a dose-ranging phase II trial in 167 people showed that MK-0518 + OBR at all three doses studied (200 mg, 400 mg, and 600 mg orally BID) had greater antiretroviral activity than placebo plus OBT. Participants were failing ART and had virus resistant to at least one drug in each of

the three available classes of oral ARVs. Merck's multicenter, randomized, double-blinded, dose-ranging, placebo-controlled study compared MK-0518 + OBT to placebo + OBT in reduction in HIV viral load, improvement in CD4 cell count, safety and tolerability. At entry, trial participants had taken ART for at least three months, had viral load levels above 5,000 copies/mL and CD4 counts over 50 (Grinsztejn 2006). At week 16, the proportion of people with viral load below 400 copies/mL ranged from 64-84% for MK-0518 vs. 22% for placebo, with 56-72% of those on MK-0518 achieving HIV RNA<50 copies compared to. 19% of those on placebo.

Merck is moving forward with the 400 mg BID dose to maintain efficacy and a high barrier to resistance while attempting to minimize side effects. Less than two years after the first MK-0518 dose in humans, Merck's phase III studies (BENCHMRK-1 and -2) are fully enrolled.

Table 1. New Anti-HIV Drugs in the Clinical Pipeline, July 2006						
	NRTIs	NNRTIs	Protease inhibitors (PIs)	Entry inhibitors (EIs)	Other mechanisms	Integrase inhibitors
Phase I	KP-1461 (KP-1212 prodrug) mutagenic nucleoside Koronis		PPL-100 Ambrilia TAK-652, Takeda 004, mAb, Human Genome Sciences	BMS-378806 gp120 blocker BMS	BI-201, Tat inhibiting mAb BioInvent	GSK364735 GSK/Shionogi
Phase Ib/II	Racivir (PSI 5004) Pharmasset Apricitabine (AVX 754) Avexa Elvucitabine (ACH-126) Achillion	BILR 355/r BS, Boehringer Ingelheim		AMD-070, CXCR4 antagonist, Anormed PRO-140, mAb, Progenics	Valproic acid, ACTG (Depakote)	
Phase II		Rilpivirine (TMC-278), Tibotec/J&J	Brecanavir/r (640385) GSK	Vicriviroc, CCR5 antagonist Schering Plough TNX-355, Anti-CD4 MAb, Tanox/Biogen	Bevirimat (PA-457 Budding inhibitor Panacos	GS-9137, Gilead
Phase III		Etravirine (TMC125) Tibotec/J&J		Maraviroc CCR5 antagonist Pfizer		MK-0518 Merck

Phase II

In phase II clinical trials, an investigational treatment is given to a group of people (100-500) to evaluate its safety and to begin to look at whether it is active/effective. Doses are often refined during phase II. In HIV drug development, phases II and III are occasionally merged. Sometimes, FDA—as it did with Merck's indinavir in 1996 and with Tibotec/J&J's darunavir ten years later—specifically requests that a company submit a new drug application (NDA) before phase III studies have been completed.

Entry Inhibitors

Progenics announced that PRO542 (a recombinant CD4-IgG2, a soluble CD4 receptor) will not be going forward, but PRO140, a similar monoclonal antibody that binds at gp120 administered via infusion, will proceed in its place. A dose-ranging study presented at CROI 2006 showed a serum half-life of around two weeks. Cells stayed coated with PRO140 for 60 days post-treatment. The study did not detect emergence of anti-PRO 140 antibodies (Olson 2006).

Schering's vicriviroc (VCV) is a CCR5 inhibitor that was being studied in both ARV-naive and ARV-experienced people. The naive trial was recently stopped due to vicriviroc/AZT/3TC inferiority to efavirenz/AZT/3TC. Virological failure on vicroviroc occurred in 22% of people on the highest dose and 56% on the low dose 25 mg arm. Schering's final analysis suggested that neither tropism shift nor resistance to VCV fully explained the virological breakthroughs (Greaves 2006). It is possible that the sponsor studied an inferior dose. The naïve trial was halted and studies in this population are on hold pending re-evaluation of the optimal starting dose.

Another dose-ranging study of 5, 10 and 15mg per day with optimized background regimen (OBR) plus ritonavir is being conducted in an ART-experienced population. The 5 mg arm was recently stopped due to worries about efficacy. Over the last few months, a series of reports of malignancies in people on the trial—occurring at five times the rate seen in similar populations not taking the drug—has Schering on tenterhooks. Besides the more common cancers that might be expected in a salvage population (skin cancers, Kaposi's sarcoma), investigators reported Hodgkin's and non-Hodgkin's lymphomas and at least two other types of cancer. Schering's plans for the middle term are fragile at best. The company must walk the tightrope between dosing (doses must be high enough to avoid virological failure) and toxicity (if cancers reach an excess rate, they will sound the death knell for this drug). If vicriviroc survives, it may be able to be administered with protease inhibitors such as atazanavir, indinavir, nelfinavir, and saquinavir without dose adjustment (Sansone 2006).

TNX-355, from Tanox, is a monoclonal antibody that competes with HIV for binding CD4. It is a large molecule that requires intravenous infusion, once per week, or, once every two weeks after week eight. TNX-355, which binds to domain 2 of the CD4 receptor, was studied in 82 treatment-experienced persons who had failed at least one ART combination. Twenty-four week data showed that 10 mg and 15 mg doses were both effective (Norris 2005). The difference between 10 mg and placebo (both + OBR) was significant (-1.19 $\log_{10}$ vs. -0.32 $\log_{10}$). Only 55% of patients on 10mg achieved an undetectable viral load at 24 weeks. At 48 weeks, the 10 mg dose had plateaued and people taking the drug achieved a -0.96 $\log_{10}$ reduction in viral load and average CD4 increases of 48 cells (Tanox 2006). Selection bias may be a factor in this 48-week open-label extension. In a study presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Tanox investigators demonstrated that TNX-355 had activity against R5-tropic, X4-tropic, and dual/mixed HIV strains in vivo. At CROI 2006, they tried to characterize each person's virus: 62.8% were R5-tropic, 2.5% exhibited X4 tropism, and 34.6% had mixed tropism. Susceptibility to TNX-355 was similar for all viruses, regardless of tropism due to the antibody's activity on CD4 rather than on co-receptors (Duensing 2006).

AMD-070 is a CXCR4 inhibitor that would seem to be a natural complement to CCR5 inhibitors for use in treating individuals with X4-predominant or mixed-tropic HIV populations and—if R5 inhibitors induce viral tropic switches—to delay or limit the emergence of X4 HIV. By itself, AMD-070 could be used in advanced individuals with an X4 or mixed or HIV population. Though AMD-070 showed preliminary activity against HIV with multiple resistance mutations (Schols 2005), toxicities in dogs caused the ACTG ten-day dose ranging trial to be suspended (NIH 2006). Anormed, another company, has now announced its own trial (PRNewswire 2006).

RTIs

Elvucitabine (Achillion) treats HIV resistant to 3TC or FTC due to the 184V mutation in reverse transcriptase. Opinions vary about whether this mutation is a bad thing, and 3TC monotherapy is being studied as a "hold on 'til something new comes along" salvage regimen in several settings (Castagna 2006). Formerly known as ACH-126, elvucitabine is an L-cytosine nucleoside with potent *in vitro* anti-HIV activity and a long (>100 hours) half-life. At doses greater than 50 mg/day, elvucitabine was associated with bone marrow toxicity and decreased white blood cells.

Pharmacokinetic/pharmacodynamic modeling suggests that lower daily doses may be effective and less-toxic (Pottage 2004). Twenty-four HIV-infected study participants received elvucitabine 5 or 10mg once daily or 20 mg every two days for 21 days with lopinavir/ritonavir BID. Elvucitabine was active and less toxic at these new doses. At day 21, HIV RNA decreased 1.8, 1.9 and 2.0 $\log_{10}$ for the 5 mg QD, 10 mg QD and 20 mg dose cohorts. No safety issues or resistance mutations were reported during these trials. Modeling suggests that once or twice weekly dosing is possible (Collucci 2005). A small 14-day, once-daily dosing trial began in March 2006 in people with the M184V mutation (ClinicalTrials.gov ID #NCT00312039).

Tibotec has fully enrolled a 320 person three-dose study of rilpivirine (RPV, formerly TMC278) compared with efavirenz in ART-naïve persons (ClinicalTrials.gov ID #NCT00110305). Rilpivirine is a diarylpyrimidine non-nucleoside RTI whose exposure increases 40% with food; Lopinavir/r raises rilpivirine's area under the curve (AUC) by over 50%, but since rilpivirine has a good pharmacokinetic profile, it doesn't need to be ritonavir-boosted. RPV is both a substrate and inducer of CYP3A4 (van Heeswijk 2006), which may complicate its use in the real world. In earlier studies, grade 3 nausea and lowering of white blood cells and neutrophils occurred in a few patients. Mild headache, fatigue, nausea and somnolence were also reported. Rilpivirine has a relatively high genetic barrier to resistance for an NNRTI but is completely cross-resistant to etravirine, Tibotec/J&J's NNRTI in phase III (de Bethune 2005).

Integrase Inhibitors

Gilead is persistently exploring integrase inhibitors. One recent compound, GS 7340, failed to move forward. GS 9137 is now in phase II, and recently the company began phase I trials of a third, GS 9160. Gilead licensed GS 9137 from Japan Tobacco in March 2005. This strand transfer inhibitor's peak blood levels and half-life are significantly increased by food. *In vitro*, the inhibitor exhibits synergy with 3TC and AZT/3TC, and is additive with AZT, tenofovir, tenofovir/3TC, efavirenz, indinavir, and nelfinavir.

Gilead's late-breaker at CROI 2006 showed reductions in viral load among people receiving GS 9137 alone or with ritonavir. This phase I/II study was a double-blind, randomized, placebo-controlled monotherapy study to evaluate the safety, tolerability and antiviral activity of GS 9137 in treatment-naive and treatment-experienced patients. Forty patients were randomized; 30 received one of five doses of GS 9137 and ten took placebo for ten days. The study evaluated 200 mg, 400 mg, 800 mg (all BID), 800 mg QD, and 50 mg/100r QD. At entry, people had a mean viral load of 4.75 $\log_{10}$ and mean CD4 cell count of 442.

GS 9137 is metabolized via CYP3A4 (with minor glucoronidation). Monotherapy demonstrated significant antiviral activity at all doses, but the lowest dose (50 mg boosted with 100 mg/r' QD) did as well or better than each of the unboosted doses up to 800 mg BID. Ritonavir boosted exposure by twenty-fold and increased trough levels ninetyfold, and prolonged the drug's half-life from 3.5 to 9.5 hours. Adverse events were grade 1-2 and resolved on treatment (de Jesus 2006). GS-9137/r will move into phase II clinical testing with dosing of 20mg/r, 50 mg/r, and 125 mg/r once daily in treatment-experienced people (Kearney 2006).

Protease Inhibitors

Brecanavir/r (formerly 640385) is GSK's third attempt at inhibiting the protease step of HIV's lifecycle, after its collaborations with Vertex on amprenavir (Agenerase) and fosamprenavir (Lexiva). One can speculate that too many mergers, too fast, slowed down the one-time pioneer of antiretroviral therapy who brought the term 'better together' to market in the mid-1990s with Combivir, the first fixed-dose combination, still a backbone of therapy worldwide. However, after Burroughs merged with Glaxo, its virologist David Barry left to found Triangle (discoverer of 3TC), which was later bought by Gilead. Other researchers left as well, development programs were canceled or delayed, and entropy set in. GSK's recent sluggish ARV drug development efforts may well represent one of the stronger arguments against excessive pharmaceutical concentration.

In an open-label study of 30 HIV-infected persons with brecanavir/r, 81% achieved viral load below 400 copies/mL at week 24. Little toxicity or resistance data have been presented or published to date. One pharmacokinetic study reported a 32% increase in exposure to tenofovir, an issue that may require closer monitoring, especially in people with slow renal clearance (Ford 2006). Brecanavir can be taken with lopinavir/r (Ford 2006). When co-administered with atazanavir, brecanavir levels rise 40%, atazanavir levels rise 44%; drug discontinuations and total bilirubin levels were higher in the triple mix (ATV + BCV/r); the authors recommend dose adjusting ATV (Ford 2006). Just one other PI—Ambrilia's PPL-100, in phase I—is in the clinic. Are protease inhibitors becoming passé?

Maturation Inhibitors

Maturation is a collection of steps near the end of the replication cycle that includes assembly, budding or extrusion (where the cell wall is disrupted and new immature HIV particles begin to leave the cell), and maturation (where the new viral proteins assume their final, infectious state).

Panacos' Bevirimat (formerly known as PA-457) is the first candidate drug to inhibit viral maturation by blocking cleavage of CA-SP1, the final step in the processing of the HIV Gag protein. The resulting virus particles are structurally defective and non-infectious. The drug was administered as monotherapy to HIV-infected subjects in a phase II trial. Thirty-two adults received ten days of placebo or daily oral PA-457 at 25, 50, 100, or 200 mg. A loading dose (double the maintenance dose) was administered on day one in all but the 200 mg cohort. HIV RNA and drug concentrations were determined over 21 days. Bevirimat exhibited linear pharmacokinetics, with a long mean half-life of 62.7 hours. It demonstrated significant antiviral activity at the higher dose levels. The maximum tolerated effect was not reached at 200 mg (Smith 2006). The amino acid positions associated with resistance to bevirimat *in vitro* are highly conserved in HIV-1 isolates, suggesting that there may be a fitness cost to resistance (Adamson 2006). Panacos continues discovery work on additional maturation inhibitors.

Phase I

Phase I studies are the earliest trials in humans. Researchers test a new treatment in a small group of people (10-50) for the first time to evaluate its safety, starting with a single dose study followed by multiple dose studies using ascending doses. Subsequent phase Ib trials in HIV-infected people help determine a safe, active range of doses, and identify initial, acute side effects.

Entry Inhibitors

BMS-378806 is a small molecule that attaches to gp120, causing a conformational change that disrupts the connection to the CD4 receptor. The compound continues to be tested but has not made notable progress over the past year.

Preclinical studies of Human Genome Science's CCR5-inhibiting monoclonal antibody (mAb) 004 show that it binds specifically and with high affinity to human CCR5, prevents HIV-1 entry, inhibits cell-cell fusion and viral transmission, demonstrates no agonistic activity or effector functions, and has a prolonged serum half-life (Roschke 2004). An *in vitro* search for resistance+- presented at CROI 2006 showed no resistance after 24 weeks and 33 passages. Although they did not find resistance, they started to notice a tropism shift to X4 virus at week 20–later confirmed at week 24–in a cell line. (Giguel 2006). Last year HGS began dosing patients in a phase I clinical trial to evaluate the safety, tolerability and pharmacology of a CCR5-inhibiting monoclonal antibody (mAb) monotherapy in HIV-infected patients (HGS 2005; NCT00114699). The study is evaluating safety and tolerability of escalating doses of a single intravenous infusion, looking at pharmacokinetics, effect on plasma HIV-1 viral load and on CD4 and CD8 T cell counts over time. No data have yet been published.

Clinical Trials Transparency
Recently, the World Health Organization (WHO) added its name to a growing roster of preeminent institutions including *The Lancet* and others urging the registration of all clinical trials. This registration and subsequent "full disclosure of key information at the time of registration are fundamental to ensuring transparency in medical research and fulfilling ethical responsibilities to patients and study participants," said Dr. Timothy Evans, assistant director-general of WHO (Mandelbaum-Schmid 2006). TAG strongly supports this initiative for a global registry platform, as well as the recent Enzi-Kennedy bill in the Senate that would make transparency, safety and limits on advertising law in the U.S., enforceable by FDA (Kaiser Network 2006).

Other Mechanisms

BioInvent's first human trial with Tat protein blocking antibody BI-201 in naïve HIV-infected patients saw no effect on viral load and no negative adverse events. Investigators will raise the dose and administer it to more patients in a second trial (BioInvent 2006) to better assess its activity and safety.

RTIs

BILR-355 from Boehringer Ingelheim is now BILR-355/r. A recent dose escalation trial of this new agent showed that ritonavir increases its area under the curve 15-30 fold, the serum peak levels increase 2-5 fold, and the half-life increases fourfold (Huang 2006). Next, BI plans to open a dose-ranging trial with triple regimen background containing either lopinavir/r or tipranavir/r (ClinicalTrials.gov NCT00294372). Enrollment will be slow unless they change their comparator PI.

KP-1212, Koronis' mutagenic nucleoside has finished phase I with no consistent toxicities or mitochondrial effects noted. FDA allowed the company to move forward (Koronis 2005). Unlike currently approved HIV treatments that work to block virus activation and replication, KP-1461 (KP-1212's pro-drug) binds at a unique site on reverse transcriptase and employs HIV's furious mutation rate to force the production of a non-functional virus. Koronis has shown the drug is synergistic with AZT and not-cross-resistant to AZT, 3TC, ABC or d4T (Harris 2005). They are currently enrolling a 40-person phase Ib study (ClinicalTrials.gov NCT00129194).

Pharmasset's racivir appears active against the M184V mutation seen in 3TC/FTC failures and contributes a 2.0 $\log_{10}$ reduction of viral load within a triple regimen (Pharmasset 2004). A 60 person trial in 3TC failures will close this summer; NRTI mavens eagerly await fall results (ClinicalTrials.gov NCT00121979). Avexa's apricitabine (AVX 754; formerly known as SPD-754) also seems active against 3TC/FTC resistant virus. Avexa's trials are designed to look at second-line use (NCT00126880). The world eagerly awaits news from a recent study of its cardiovascular safety (ClinicalTrials.gov NCT00334659).

Protease Inhibitors

Ambrilia Biopharma recently bought PPL-100 from ProCyon and completed a phase I study. The only information about this drug (as with many phase I agents) comes from a press relesae touting it as not requiring ritonavir boosting. Ambrilia will move forward with a phase Ib study, investigating safety and pharmacokinetics after repeated oral dosing in both the 600 mg and 1200 mg doses given once daily with and without low-dose ritonavir (which raises AUC by approximately 60%). Results are expected in early 2007. PPL-100 has a long (20-36 hour) half-life. *In vitro*, it shows no cross-resistance to most other PIs and hyper susceptibility to some (Wu 2006).

Multi-Experimental Drug Studies (MEDS)

For people with multidrug-resistant HIV, the decision about when to switch to a new combination regimen likely to be effective--or what to do while waiting can be agonizingly difficult. It isn't clear who would benefit from early switches to partially effective new regimens versus waiting on a combination including 3TC or FTC even in the presence of the M184V mutation. Deeks and colleagues have shown that even with resistance to all three classes including to 3TC, some people better maintain a less fit, less pathogenic virus when they stay on partially effective regimens (Deeks 2005).

Another option would be taking more than one experimental drug at the same time, assuming they were available. In 1999 FDA announced that trials with multi-experimental agents are viable for registration (FDA 1999) and made it easier to gain approval for new drugs studied in a pre-treated population. Most anti-HIV drugs approved since then used this method to gain a quick foothold in the market, citing the need for safe and effective treatments in a heavily experienced population; see lopinavir/r, tenofovir DF, T-20, tipranavir/r, and now darunavir/r.

In the pivotal studies of tipranavir/r and darunavir/r, having a second active new drug (such as T-20) available when switching to the new drug has been shown to nearly double the virological success rate among heavily treatment-experienced individuals.

A dual experimental combination agent trial could answer the golden question: Are these two (or more) experimental agents useful together? It may prevent virtual monotherapy for people in salvage settings. Variables that need to be addressed include resistance and cross-resistance, choice of optimized background regimen (OBR), the use/availability of newer drugs not directly being studied, and drug interaction/PK studies. If these questions can be answered before phase III, there is no reason for standard phase III trials not to allow concomitant use of other investigational agents (Benchmrk 2006).

Ever since the community first proposed the ARISTO study in 1999 (A Randomized Study of Salvage Treatment Options), in which three experimental agents would be evaluated together (James 1999), there has been interest in studies utilizing several experimental agents simultaneously. Feasibility of this approach has been limited by non-synchronous drug development timelines, the disinclination of sponsors to work together, and the lack of appropriate drug-drug interaction data to guide dosing regimens in such a study.

ARISTO-type studies would be able to help define the use of several new salvage therapy drugs simultaneously while avoiding the exposure of any study participants to virtual monotherapy. Important strategic answers can be achieved without sacrificing trial volunteers to multidrug-resistance. In 2005, FDA reaffirmed its willingness to countenance the implementation of such studies (Struble 2005). Tibotec was the first company to attempt this trial design. Since the company had two drugs close enough in development, investigators did not need to negotiate with another company. The result: the DUET studies, which are registration trials examining darunavir/r and etravirine simultaneously in semi-treatment experienced and heavily experienced populations. Although imperfect and not without risks, DUET has opened the door for other companies to consider similar phase III designs.

If any company is interested:

> Ambrilia's SPC3 [a putative fusion inhibitor] is available for licensing to partners interested in co-development and commercialization… *In vitro*, it has been shown to inhibit viral replication in human lymphocytes and macrophages… The lead compound has been tested in patients in two clinical studies, in London (UK) and Providence (RI - USA). Results observed at the time were disappointing, mainly because of the product's hydrophilic nature which hampered its potential in reaching target organs and cells. As a result, Ambrilia has developed a new lipophilic formulation. The *in vitro* results, on human cells, showed an inhibitory activity 10 to 100 times greater than that of the original product. (Ambrilia 2006).

Summary

Of twenty-four anti-HIV agents now in the clinical pipeline, nine are in phase II/III and likely to go before FDA in the next two years; the other fifteen are further back and have a higher likelihood of dropping out. Small biochemical companies with products in phases I and II must partner with universities if novel treatment approaches are to move forward.

The Future of Expanded Access

For a decade, since the introduction of HAART in 1996, sponsors have begun their expanded access programs (EAPs) late and kept them small through restrictive criteria. In earlier years, Burroughs Wellcome provided 5,000 late-stage AIDS patients with AZT before approval in 1987. Bristol-Myers provided ddI to over 35,000 people between 1989-1991, and over 12,000 with d4T in 1992-1994. Glaxo provided 3TC to over 30,000 people in the mid-1990s. These expanded access programs reflected the very desperate state of AIDS treatment before the advent of HAART.

More recent EAPs for drugs such as T-20 (Roche), atazanavir (BMS), tipranavir/r (BI), and now darunavir/r (Tibotec) have been much smaller and begun rather late.

Can expanded access be resuscitated as more equitable, broadly based pre-approval programs to provide access to experimental therapies for HIV-infected persons who need new treatment choices but are ineligible for, or cannot access, controlled clinical trials?

We will probably see a broadening of licensed anti-HIV therapy targets, from the very earliest stages of the HIV life cycle through the intermediate stage of integration to later stages such as maturation. This may have potential to transform strategic approaches to therapeutic management of HIV, changing when to start, what to start with, and providing new options to people with triple-class-resistant HIV.

The obstacles to a better future for people with HIV are clear. The great majority of the world's people living with HIV and growing numbers even in the U.S. still lack easy access to simple, affordable, safe and effective treatment. There are many major players in the drug development process, the pharmaceutical industry pre-eminent among them. Continued vigilance, activism, and informed advocacy are crucial to fostering more enlightened drug development, approval, and post-marketing access and availability.

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Immune-Based Therapies and Preventive Technologies Pipeline 2006

by Richard Jefferys

The Current Landscape

In the year since TAG's last pipeline report, there have been no seismic shifts in the landscape of immune-based HIV therapies and preventive technologies (vaccines, microbicides, and pre-exposure prophylaxis or PrEP). No effective precedents have emerged in any of these areas, although there have been positive developments. On the immune-based therapy front, two studies have shown a meager – but statistically significant – impact of therapeutic vaccination on viral load during treatment interruptions (Levy 2006; Bucy 2005). Both of these studies used the very poorly immunogenic ALVAC vaccine vector, which leaves open the possibility that more potent immunogens could have a greater therapeutic impact. A phase I study of IL-7, a potentially T cell-restoring cytokine, is ongoing, and new macaque data suggest that another cytokine, IL-15, is also a candidate for study in humans (Picker 2006). For the first time, an anti-HIV gene therapy – developed by Johnson & Johnson – is being evaluated for efficacy in a phase II trial.

In the preventive vaccine field, the rationale for studying vaccines that induce T cell responses against HIV has been further bolstered by recent studies using the model of macaques challenged with SIV, HIV's simian equivalent (Letvin 2006; Wilson 2006). One human efficacy trial of a T cell-based vaccine designed by Merck is ongoing, and another–due to start in the next year or so–will evaluate a vaccine constructed by investigators at the National Institutes of Health's Vaccine Research Center (VRC). Encouragingly, these studies promise to complement each other: the Merck vaccine includes the gag, pol, and nef genes from HIV, while the VRC construct incorporates gag, pol, nef plus three different env genes from HIV-1 subtypes A, B, and C. There is an ongoing debate in the vaccine field about the value of including the env gene, so these trials promise to provide valuable information. Additionally, the Merck vaccine employs an adenovirus serotype 5 (Ad5) vector, while the VRC approach uses a DNA vaccine as a "prime" followed by an Ad5 vector as a "boost." Given that the HIV vaccine efficacy trials conducted to date have been based on thin scientific rationales and have contributed little useful information to the field, the Merck and VRC trials represent significant strides forward.

Microbicide research has continued its gratifying march from the margins into the mainstream. The recent Microbicides 2006 conference in Cape Town, South Africa drew over 1,300 participants to discuss the state of the field. Currently there are several ongoing efficacy trials of microbicides, although the products involved are not likely to be more than partially effective, at best. There is more optimism about the next generation of products that target HIV more specifically, such as co-receptor inhibitors and HIV reverse transcriptase inhibitors. These products are in earlier phases of study.

Research continues on the potential efficacy of Pre-Exposure Prophylaxis (PrEP) with the antiretroviral drug tenofovir (Viread®), despite the premature cessation of trials in Cambodia, Cameroon, and Nigeria. Preliminary data from these trials, and the remaining ongoing study in Ghana, are expected at the International AIDS Conference in Toronto. Meanwhile, plans are well underway for a National Institutes of Health-funded study of PrEP in Peruvian gay men. The Peruvian trial may employ a pill (Truvada) that combines both tenofovir and emtricitabine, due to the significant and sustained protection seen with this combination in the SIV/macaque model (Garcia-Lerma 2006).

Preventive Technologies: Vaccines

Results from the Merck and VRC trials will represent a critical milestone for the HIV vaccine field. Should the T cell responses induced by these vaccines fail to offer any significant protection against infection or disease progression, the prospects for almost all of the other vaccine candidates in earlier stages of development will be exceedingly grim. Conversely, if some significant degree of protection is observed, researchers will finally have a base on which to try and build more effective vaccine strategies. Only a handful of candidates under clinical evaluation aim to induce antibody responses, and there is not much

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 6-24 hours later antibodies that bind to a specific cytokine are introduced. The cells are chemically treated so that any antibodies bound to cytokine-producing cells are stained blue and can be counted. They're called "spot-forming cells" or SFC for short. Background cytokine production (i.e. production that occurs without any antigen stimulation) can be a problem, and must be subtracted to assess how many T-cells were specifically responding to the antigen.

Intracellular Cytokine Staining (ICS): ICS 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. This allows the precise type of T-cell that is making a given cytokine to be more easily identified.

The cytokine most commonly measured in these assays is interferon gamma but more studies have recently begun to look at additional cytokines and chemokines, particularly IL-2. This shift was prompted by studies showing that vaccine-induced T cells typically comprise a mixed population, only a small proportion of which make interferon-gamma (De Rosa 2004). This contrasts with chronic infections like CMV, where a much larger proportion of the detectable T cell response is typically able to produce interferon gamma.

optimism about their prospects; the induction of broadly neutralizing antibodies remains the most sterling challenge facing the vaccine field.

Despite the lack of major scientific developments in vaccine research, new human immunogenicity data exist for some of the T cell-based vaccines being evaluated by the National Institutes of Health-sponsored HIV Vaccine Trials Network (HVTN). These data were revealed by HVTN director Larry Corey at the 13th Conference on Retroviruses and Opportunistic Infections (CROI) in 2006. Unfortunately, the news was disappointing.

By contrast, the adenovirus vectors developed by Merck and VRC are capable of inducing HIV-specific T cell responses in upwards of 50% of recipients (Isaacs 2004). However, there may be problems associated with using solely interferon gamma as a readout when measuring T cell responses (see box), so these data are not necessarily the death knell for all the listed constructs. Additional analyses of parameters such as IL-2 production are ongo-

Vaccine	ELISpot assay for interferon-gamma production (# of positive responders)
GeoVax DNA vaccine	0/28
Lipopeptides	0/23
ALVAC alone	1/24
ALVAC+lipopeptides	3/77
ALVAC vcp1452 low dose	2/37
ALVAC vcp1452 high dose	5/52
VEE	0/35
Epimmune multi-epitope DNA	1/26
Chiron DNA	8/50
Wyeth multi-epitope peptides	0/65
CMV control peptides (all trials)	50-70%

Source: Corey 2006, webcast online at:: www.retroconference.org/2006

ing. It's also possible that a vaccine with borderline immunogenicity might still serve as a priming immunization, if followed by an appropriate booster shot (the GeoVax DNA vaccine, for example, is being evaluated as a potential priming vaccine in tandem with an MVA boost).

Although the scientific landscape for vaccines looks much the same as it did a year ago, changes have occurred in the terrain of public policy. The National Institutes of Health awarded a large grant (potentially totaling more than $300 million over seven years) to a consortium led by Barton Haynes at Duke University, dubbed the Center for HIV/AIDS Vaccine Immunology (CHAVI). CHAVI's stated goal is to "to solve the major problems preventing the development of a safe and effective HIV vaccine." The consortium's research plan is based around an R01 grant to Haynes to study transmitted HIV isolates, the

generation of T cell responses in acute/early HIV infection, and genetic factors influencing both the risk of acquiring HIV and the progression of disease. Additional investigators participating in CHAVI are conducting complementary individual projects: George Shaw from the University of Alabama, who has conducted extensive studies on antibody responses during acute and early HIV infection, is researching the neutralization properties of transmitted HIV isolates. A researcher with expertise on the structure of HIV's envelope proteins, Joe Sodroski, is investigating the envelope trimers on transmitted viruses. Harvard's Norman Letvin, who has published extensively on the efficacy of vaccination in macaques challenged with SIV, has been charged with evaluating the correlates of immune protection in this model.

CHAVI will participate in the Global Vaccine Enterprise, another relatively new player in the arena of HIV vaccine policy. The Enterprise was proposed in 2003 by a diverse group of researchers and community advocates (Klausner 2003) and endorsed by the G-8 in 2004. It is now hosted by the Bill & Melinda Gates Foundation, which has committed up to $300 million over five years to support Enterprise activities. The Enterprise aims to follow the model of the Human Genome Project, acting as an overall coordinating mechanism for the HIV vaccine field. Dr. Adel Mahmoud, former president of Merck Vaccines, was appointed Chief Executive in September 2005. The National Institutes of Allergy and Infectious Diseases (NIAID) Council recently allocated seven million dollars over seven years to support Mahmoud's work at the Enteprise. So far the Enterprise has published a Scientific Strategic Plan (Global HIV/AIDS Vaccine Enterprise 2005) but is still too new an entity to have produced any concrete contributions to the field. Still, there are signs of improved collaboration in the vaccine field, and discussions that occurred leading up to the launching of the Enterprise may well have played a role in fostering it.

Desired Elements of Vaccines

The ideal attributes of a preventive HIV vaccine can be quickly summarized:

- Complete protection against HIV infection in as many recipients as possible
- Effective against multiple HIV subtypes
- Long-lasting immunity
- Easy to manufacture on a large scale
- Easy to deliver (e.g., a single shot)
- Easy to ship and distribute globally
- Effective against multiple HI
- Cheap
- Safe

A Note on Antigens and Subtypes

An important aspect of vaccine design is deciding which parts of HIV (HIV "antigens" in immunological parlance) the vaccine should induce immune responses against. HIV contains a total of nine genes (env, gag, pol, nef, tat, rev, vpr, vif, vpu), all of which encode proteins that are potential targets for the immune system. Specialized immune system cells called antigen-presenting cells (APCs) break down proteins into small slices called epitopes that can be recognized by individual T cells, and some vaccines include known epitopes from particular HIV proteins rather than (or in addition to) using the whole protein. As evidenced by the vaccine pipeline table, a diverse array of HIV antigens are being employed in current HIV vaccine studies. For example, Merck has selected the gag, pol and nef genes for their Ad5 vaccine candidate. This decision was based on extensive studies of HIV-specific T cell responses in infected individuals which showed that the proteins encoded by these genes are the most frequently targeted (Coplan 2005).

Merck also based its decision on the relative conservation of these genes across different HIV subtypes. Subtypes are a way of classifying HIV based on the virus's genetic make up. For example most viruses from North America and Europe are genetically similar and are said to belong to HIV subtype B. Many viruses found in Africa are also similar but show distinct genetic differences from HIV subtype B and are therefore classified as belonging to different subtypes (subtypes A, C, and D are the most common in Africa). Mixes between different subtypes are called circulating recombinant forms (CRFs), for example the prevalent HIV in Thailand was once classified as belonging to subtype E but is now designated as a mix between subtypes A and E called CRF01_AE. The genetic variability of HIV globally presents a major challenge for vaccine developers because immune responses that recognize HIV from one subtype may fail to recognize viruses from other subtypes. Hence Merck's focus on genes from HIV that are very similar from subtype to subtype (in general, HIV's env gene varies the most while gag is the most conserved). While most vaccine candidates were initially based on HIV subtype B, an increasing number now include HIV components from alternative or multiple subtypes.

Preventive HIV Vaccines			
Product	**Type**	**Manufacturer**	**Status**
ALVAC vCP1521	Canarypox vector encoding: HIV-1 CRF01_AE env, subtype B gag, the protease-encoding portion of the pol gene and a synthetic polypeptide encompassing several known CD8 T-cell epitopes from the Nef and Pol proteins	Aventis Pasteur	Phase III Phase I (in infants)
ALVAC vCP1452	Canarypox vector encoding portions of subtype B HIV-1 env, gag, pol and a synthetic polypeptide encompassing several known CD8 T-cell epitopes from the Nef and Pol proteins	Aventis Pasteur	Phase II
AIDSVAX B/E (booster only)	Recombinant gp120 envelope protein	VaxGen	Phase III
MRKAd5	Adenovirus serotype 5 vector containing gag/pol/nef genes from HIV-1 subtype B	Merck	Phase IIb
LIPO-5	5 lipopeptides containing CTL epitopes (from Gag, Pol and Nef proteins)	ANRS; Aventis	Phase II
GTU-Multi-HIV	DNA vaccine containing nef, rev, tat, gag, pol, env, and CTL epitopes	FIT Biotech	Phase I/II
pHIS-HIV-B rFPV-HIV-B	DNA vaccine + fowlpox boost containing gag, rev, tat, vpu, and truncated env genes from HIV-1 subtype B	University of New South Wales, Australia, Virax	Phase I/II
ADMVA	MVA vector containing env/gag-pol, and nef-tat genes from HIV-1 subtype C	Aaron Diamond AIDS Research Center (ADARC), IAVI, IDT	Phase I
GSK Protein HIV Vaccine	Recombinant Tat, Nef, and gp120 proteins in ASO2A adjuvant	GlaxoSmithKline	Phase I
VRC-HIVADV014-00-VP	Adenovirus serotype 5 vector containing gag/pol genes from HIV-1 subtype B and env genes from subtypes A, B, and C	NIH Vaccine Research Center	Phase II
AdVax 101 (VEE)	Venezuelan Equine Encephalitis virus vector containing the gag gene from HIV-1 subtype C	AlphaVax	Phase I
VRC-HIVDNA016-00-VP	Six separate DNA plasmids containing gag, pol, and nef genes from HIV-1 subtype B, and env genes from subtypes A, B, and C	NIH Vaccine Research Center	Phase II
TBC-M358 (MVA) TBC-M335 (MVA) TBC-F357 (FPV) TBC-F349 (FPV)	MVA and fowlpox vectors encoding env, gag, tat, rev, nef, and reverse transcriptase genes from HIV-1 subtype B	NIAID, Therion	Phase I
LIPO-4T (LPHIV-1)	4 lipopeptides containing CTL epitopes (from gag, pol-RT, pol, and nef)	ANRS, Biovector SA	Phase I

LFn-p24	Anthrax-derived polypeptide LFn Gag p24 protein	AVANT, NIAID, WRAIR	Phase I
HIV CTL MEP + RC529-SE and GM-CSF adjuvants	DNA vaccine containing CTL epitopes from env or gag	NIAID, Wyeth	Phase I
DNA + Protein Vaccine Combination	DNA vaccine containing a gag gene (from HIV-1 subtype C) and 5 env genes (from subtypes A, C, and E + two from subtype B), plus a protein boost using recombinant gp120 proteins from the same 5 isolates that supplied the env genes for the DNA component	University of Massachusetts Medical School, Advanced BioScience Laboratories, Inc.	Phase I
tgAAC09 AAV	Adeno-associated virus vector containing gag, protease, and reverse transcriptase genes from HIV-1 subtype C	Targeted Genetics, IAVI	Phase II
ADVAX DNA	DNA vaccine containing gag, env, pol, nef, and tat genes from HIV-1 subtype C	IAVI, ADARC, Vical	Phase I
DNA/PLG Oligomeric gp140/MF59	DNA vaccine containing gag and env genes from HIV-1 subtype B, plus a protein boost containing a gp140 protein also from subtype B	Chiron	Phase I
VRC-HIVDNA-009-00-VP	DNA vaccine containing gag, pol, and nef genes from HIV-1 subtype B, and env genes from subtypes A, B, and C, together with an adjuvant gene encoding an IL-2 fusion protein	VRC, HVTN, Vical	Phase I
PolyEnv1	Vaccinia viruses expressing 23 different env genes	St. Jude Children's Research Hospital	Phase I
EnvDNA	DNA vaccine encoding multiple env genes	St. Jude Children's Research Hospital	Phase I
ISS P-001	Recombinant Tat protein from HIV-1 subtype B	ISS, Excell	Phase I
EP HIV-1090 DNA EP-1043	DNA vaccine containing 21 CTL epitopes from gag, pol, env, nef, rev, and vpr (HIV-1 subtype B) + recombinant protein vaccine designed to induce CD4 T cell responses	NIAID, Epimmune	Phase I
HIV DNA vaccine + IL-12	DNA vaccines encoding HIV-1 subtype B gag and IL-12	NIAID, Wyeth	Phase I
HIV DNA vaccine + IL-15	DNA vaccines encoding HIV-1 subtype B gag and IL-15	NIAID, Wyeth	Phase I
pGA2/JS7 DNA MVA/HIV62	DNA prime and MVA booster vaccines encoding gag, pol and env from HIV-1 subtype B	NIAID, Geovax	Phase I
SCBaL/M9 Soluble subunit protein	Oral vaccine utilizing salmonella typhi encoding gp120-CD4, subunit protein vaccine containing the same gp120-CD4 protein	Institute of Human Virology	Phase I

Adenovirus-Based Vaccines

As outlined in the introduction, the two vaccine approaches that are currently considered most promising 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. One of the features of adenoviruses that make them ideal vaccine vectors is their targeting of dendritic cells, which are responsible for initiating T cell responses.

Unfortunately, Ad5 vectors do have a potential Achilles heel. 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. It's estimated that about one third of North Americans have high levels of neutralizing antibodies targeting Ad5 (defined as an antibody titer >1:200); in the developing world, the proportion approaches 90% (Kostense 2004). The first studies of Merck's prototype Ad5 vector, encoding only the HIV Gag protein, demonstrated that high antibody titers against Ad5 severely reduced the ability of the vector to induce Gag-specific T cell responses. Only around 20% of participants with anti-Ad5 antibody titers >1:200 developed T cell responses. For this reason Merck's 1,500-person phase IIb efficacy trial (a collaboration with HVTN that began in 2004) initially excluded individuals with anti-Ad5 antibody titers greater than 1:200.

Over the last year, however, data emerged from trials utilizing Merck's newer Ad5 construct, which encodes three HIV proteins: Gag, Pol and Nef. For reasons that are unclear, high levels of anti-Ad5 antibodies had less of an impact on the induction of T cell responses by this version of the vaccine. Due to these results, Merck and HVTN decided to add another 1,500 people to the phase IIb trial, irrespective of their anti-Ad5 antibody levels (Isaacs 2005). If neutralizing antibodies against Ad5 turn out to be problematic, a recently published study has shown that it is possible to create a modified Ad5 vector that can evade antibodies by replacement of the viral hexon protein (Roberts 2006).

The NIH's Vaccine Research Center (VRC) has developed another Ad5 vaccine candidate consisting 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. VRC is testing this vaccine both alone and as a booster to its DNA vaccine which encodes the same proteins plus subtype B Nef. The DNA vaccine also uses a separate DNA plasmid to encode each protein. In early studies, this approach proved better at inducing T cell responses to each component as compared to plasmids that encoded multiple proteins (Graham 2005a). Phase I evaluations of Ad5 at various doses (109, 1010, 1011, with ten people receiving each dose) demonstrated the induction of CD8 T cell responses in the majority of participants; the highest dose also caused mild systemic symptoms (such as fever and chills) in about half the recipients. Giving the Ad5 vaccine as a booster following DNA immunization increased the magnitude of vaccine-induced immune responses by eleven to twenty-one-fold (Graham 2005b). An international multi-site phase II trial of the VRC's DNA/Ad5 combination was launched in October 2005 in collaboration with the HVTN, into which a total of 480 participants will enroll. In tandem, the International AIDS Vaccine Initiative (IAVI) plans to conduct a phase I study of the VRC vaccine at sites in Kenya and Rwanda, and the U.S. Military HIV Research Program is slated to conduct phase I and II studies at sites in Uganda, Kenya and Tanzania. This combined effort by four different entities marks a first for the vaccine field, perhaps providing evidence that the intensified collaboration envisioned by the Global Vaccine Enterprise is feasible. If the phase II results are encouraging, the VRC's longer term plan is to conduct a three-arm 16,000-person efficacy trial that will compare Ad5 to DNA + Ad5 to placebo, powered to detect efficacy in any vaccine arm.

ALVAC (Aventis Pasteur)

ALVAC is an HIV vaccine candidate manufactured by Aventis Pasteur that uses a bird virus called canarypox as a vector. ALVAC has the dubious distinction of being the longest-studied viral vector vac-

cine candidate, with more than 1,000 people having participated in phase I and II studies over the last ten years. Unfortunately, ALVAC induces persistent HIV-specific CD8 T-cell responses in just 10-20% of recipients (Nitayaphan 2004; Russell 2005), leading to considerable skepticism about its potential efficacy. A number of ALVAC variants have been developed in an effort to improve the immunogenic response rate, but none have proved successful. ALVAC version vCP1521 (which encodes HIV-1 CRF01_AE env and subtype B gag, the protease-encoding portion of the pol gene and a synthetic polypeptide encompassing several known CD8 T-cell epitopes from the Nef and Pol proteins) is undergoing an efficacy evaluation in a huge 16,000-person trial in Thailand initiated by researchers affiliated with the U.S. Military HIV Research Program. Results should be available within the next four years. The trial also includes a booster immunization with AIDSVAX, an antibody-based vaccine that has failed to show efficacy in two large phase III trials (Flynn 2005; Pitisutithum 2004) and is no longer manufactured by VaxGen, the company that originally designed and produced it. Many leading HIV vaccine scientists have harshly criticized the planning and design of this ALVAC/AIDSVAX trial, as has TAG (Burton 2004; Jefferys 2004).

Lipopeptides

Lipopeptides are synthetic fragments of viral proteins associated with lipids in order to facilitate the induction of T cell immune responses. Lipopeptides are difficult to manufacture on a large scale, making it uncertain whether they could ever be produced commercially. These vaccines are being developed by the French research agency ANRS, but the immunogenicity data presented at CROI by the HVTN's Larry Corey were not impressive and the future of these vaccines appears uncertain (Corey 2006).

Modified Vaccinia Virus Ankara strain (MVA)

MVA is an attenuated, nonpathogenic derivative of the cowpox virus. An MVA-based HIV vaccine candidate designed by Andrew McMichael and Tom Hanke from Oxford University has undergone extensive human testing with the support of the International AIDS Vaccine Initiative (IAVI). Unfortunately, immunogenicity was disappointing, with persistent HIV-specific CD8 T-cell responses detectable in just 10-20% of recipients (Guimaraes-Walker 2004; Jaoko 2004). As a result, IAVI is not pursuing further studies of this construct. Three other MVA-based HIV vaccine candidates (manufactured by Therion, Aaron Diamond AIDS Research Center, and GeoVax) are in human studies, but it is unclear whether they will prove more immunogenic.

DNA Vaccines

DNA vaccines are perhaps the simplest and cheapest approach to inducing T-cell responses. These constructs have proven immunogenic in mice and monkey studies, and a few years ago there was considerable optimism that they would be efficacious in humans. Data from human trials have since dimmed that optimism, with only a minority of recipients displaying low-level T cell responses to the vaccines. Scientists speculate that the problem may be a matter of size and dose: humans are simply much larger than the animals used in preclinical studies, and the dose of DNA vaccine that can be delivered is limited by the fact that the DNA becomes an unwieldy goo - difficult and painful to inject - at doses much higher than 5mg. Nevertheless, multiple DNA vaccines continue to undergo human testing. In some cases, as with the candidate being developed by VRC, the intent is to use the DNA vaccine as a "prime" before boosting with a viral vector vaccine. Another strategy under study involves adding adjuvant components (such as the cytokines IL-2, IL-12, or IL-15) to the DNA vaccine that may boost the T-cell response. Since the 2005 TAG pipeline report, two new DNA vaccines with cytokine adjuvants (IL-12 and IL-15) have entered human testing through the HVTN. These vaccines are manufactured by Wyeth, which recently hired Emilio Emini – formerly head of vaccine research at Merck and IAVI – to run its vaccine program.

Recombinant Proteins

Several years ago, just after Merck announced the launch of its HIV vaccine program, GlaxoSmithKline (GSK) chimed in with a press release touting its own "new" HIV vaccine program. Observers of the field noted that the construct-recombinant HIV Nef, Tat, and gp120 proteins in a proprietary ASO2A adjuvant-was a candidate developed and then shelved by SmithKline Beecham, the company with which Glaxo had just merged. SKB discontinued the vaccine due to conflicting results from macaque challenge experiments and its apparent inability to induce CD8 T-cell responses. GSK chose to put a positive spin on these studies and has advanced the construct into phase I human testing. Preliminary results have demonstrated decent HIV-specific CD4 T-cell responses but no detectable vaccine-induced CD8 T cells (Horton 2004).

Three other vaccine candidates undergoing human trials also 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. An oligomeric protein is composed of multiple protein chains as compared to a monomeric protein, which contains a single chain (for example, AIDSVAX is monomeric gp12). Chiron is hoping that this protein will stand a better chance of inducing neutralizing antibodies against HIV. 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 (Srivastava 2003).

Advanced Bioscience Laboratories (in collaboration with the University of Massachusetts and CytRx, and with NIH support under the HIV Vaccine Design and Development Team program) is using recombinant gp120 proteins from multiple subtypes (A, C, E, and two from B) as a booster following a DNA vaccine encoding the same env genes along with HIV subtype B gag. The proteins are delivered with an adjuvant called QS21. The approach is based on unpublished animal data which apparently suggests that immunization with gp120 proteins from multiple subtypes may induce qualitatively superior antibody responses compared to those induced by gp120 from a single subtype. Unfortunately the phase I trial of this vaccine was halted by the Data Safety Monitoring Board due to a case of cutaneous small-vesicle vasculitis that developed in a single participant receiving the highest dose. The investigators are reviewing the data and hope to be able to address the toxicity issue and continue development of the vaccine (Kennedy 2005).

Maverick Italian researcher Barbara Ensoli has long been pursuing the hypothesis that a recombinant HIV Tat protein could prove effective as a vaccine. Ensoli and colleagues published a controversial study in cynomolgus macaques many years ago that claimed successful protection against a SHIV89.6P challenge using this approach (Cafaro 1999). A subsequent attempt to confirm these findings by David Watkins was unsuccessful, although the construct and approach used were not exactly matched (Allen 2002). Ensoli has now successfully moved the Tat protein vaccine into phase I human testing in Italy.

Adeno-Associated Virus (AAV)

One of the more intriguing new viral vectors to enter human trials is Adeno-Associated Virus (AAV). AAV is a parvovirus that depends on adenovirus to replicate; the vector has been further modified so that it is completely replication-incompetent. Developed by Phil Johnson at the Children's Research Institute in Columbus, Ohio, in collaboration with Targeted Genetics (with the support of IAVI), AAV displays some unique features that could prove extremely advantageous for an HIV vaccine. Specifically, AAV appears to persist and express its HIV protein payload for months after a single immunization. This feature offers the hope that, if successful, AAV could be used as a single-shot immunization. It has taken many years to advance this candidate to human testing due to

concerns that it may integrate into human DNA, but extensive safety studies in animals have now reassured regulatory authorities that it is safe to test in humans; AAV appears able to persist in episomal form without integrating. Immunogenicity results in macaques were impressive, showing a robust, dose-dependent induction of HIV-specific T-cell responses and anti-Gag antibodies (Schulz 2004; Fast 2005). In November 2005, IAVI announced the launch of a new phase II trial of an AAV-based HIV vaccine in South Africa. The 18-month trial will enroll 78 men and women. The AAV vector being used in the trial carries HIV antigens from subtype C, the most prevalent HIV subtype in southern and eastern Africa. The first human immunogenicity data from AAV trials is expected to be presented at the AIDS Vaccine 2006 conference in September.

Oral Salmonella Typhi Vector

A novel oral HIV vaccine candidate that entered clinical testing in the past year is the Salmonella enterica serovar (type) Typhi-based construct developed by George Lewis and colleagues at the Institute for Human Virology in Baltimore (Fouts 2003). Because it is administered orally, this bacterial vector – a highly attenuated version of the pathogen that causes typhoid fever – might be advantageous for inducing immune responses in the mucosa, via which the majority of HIV transmissions occur. The antigen carried by this vaccine is also novel, although somewhat controversial. It is a complex of the HIV envelope protein gp120 and part of the CD4 molecule via which HIV enters T cells. The intent is to induce antibodies targeting regions of gp120 that are only exposed while it is in contact with CD4. It remains uncertain whether these antibodies will be produced and whether they will work; there is some concern that antibodies targeting parts of CD4 (a human molecule) might carry a risk of stimulating autoimmunity. Due to this concern, study participants will be carefully monitored for signs of immune responses to CD4 epitopes.

Preventive Technologies: Microbicides

Microbicides are substances applied topically to the vaginal or rectal surface prior to sex, aiming to prevent HIV infection (and possibly other sexually transmitted infections). One major advantage to such interventions, if they can be successfully developed, is that they could potentially be used by women who may not be able to control whether or not their partner uses a condom. After a period in which microbicide research seemed to wander in something of a scientific wilderness, the past few years have witnessed a new and broadening enthusiasm for the field. As a result, the microbicide pipeline has swelled, and a number of phase III efficacy trials are now underway.

The establishment of the non-profit International Partnership for Microbicides (IPM) has also added fresh impetus to the field, in a manner akin to the way the establishment of IAVI helped fuel HIV vaccine research. Among other activities, IPM is actively seeking to license pharmaceutical compounds that may have promise as microbicides. The first such compound is already undergoing clinical testing: a gel formulation of the Tibotec reverse transcriptase inhibitor dapirivine (TMC120). Toward the end of 2005, IPM licensed two additional potential candidates, the CCR5 inhibitor CMPD 167 from Merck and the attachment inhibitor BMS-378806 from Bristol-Myers Squibb. These agents have recently shown promise as microbicides in the macaque/SIV model (Veazey 2005).

Desired Elements of a Microbicide

The four guiding principles of microbicide design are "cheap, safe, effective, acceptable" (Moore 2003). It would also be highly advantageous if a microbicide could be used 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 just 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 a microbicide over a period of days or months (Woolfson 2000).

The Current Pipeline

Product	Type	Manufacturer	Status
Carraguard®	Adsorption inhibitor	Population Council	Phase III
Cellulose sulfate (Ushercell®)	Adsorption inhibitor	Global Microbicide Project	Phase III
PRO 2000/5 Gel	Adsorption inhibitor	Indevus Pharmaceutical, Inc.	Phase III, Phase II/IIb (with BufferGel), Phase II (with tenofovir)
Savvy (C31G)	Surfactant	Cellegy Pharmaceuticals	Phase III
BufferGel™	Acid-buffering agent	Reprotect, LLC	Phase II/IIb (with PRO2000)
Lactin-V	Vaginal defense enhancer	Osel, Inc.	Phase II
Protected Lactobacilli in combination with BZK	Acid-buffering agent/surfactant	Biofem, Inc.	Phase II
Tenofovir/PMPA Gel	Reverse transcriptase inhibitor	Gilead Sciences, Inc.	Phase II/IIb (alone and with PRO2000)
Invisible Condom	Entry/fusion inhibitor	Laval University (Division of Microbiology)	Phase I/II
ACIDFORM Gel	Acid-buffering agent	Global Microbicide Project	Phase I
Cellulose acetate 1,2-benzenedicar-boxylate (cellulose cetate/CAP)	Adsorption inhibitor	Lindsey F. Kimball Research Institute, Dow Pharma	Phase I
Lime Juice	Acid-buffering agent	University of Melbourne	Phase I
TMC120	Reverse transcriptase inhibitor	International Partnership for	Phase I
UC-781	Reverse transcriptase inhibitor	Microbicides (IPM)	
VivaGel (SPL7013 gel)	Entry/fusion inhibitor	Biosyn, Inc.	Phase I
PC 815 (Carraguard + MIV-150)	Combination adsorption inhibitor/reverse transcriptase inhibitor	Starpharma Ltd. Population Council	Phase I Phase I

Microbicides in efficacy trials fall into the following categories:

Surfactants

Surfactants are detergent-like chemicals that disrupt the lipid membranes of cells and the HIV envelope. Nonoxynol-9 (N-9) is a surfactant with anti-HIV activity that was tested for efficacy as a potential microbicide in a phase III trial sponsored by the United Nations Joint Programme on HIV/AIDS (UNAIDS). Unfortunately results showed that it marginally increased the risk of HIV infection (Van Damme 2002), likely owing to its demonstrated capacity to induce vaginal inflammation (Stafford 1998). Results from this trial strongly suggest that, to be successful, a microbicide will have to be almost totally devoid of vaginal toxicity. A newer and putatively less toxic surfactant named SAVVY has been developed (Krebs 2000). SAVVY is being evaluated in an efficacy trial in Nigeria sponsored by USAID, Family Health International and the manufacturer, Cellegy Pharmaceuticals. A similar trial in Ghana had to be stopped in late 2005 due to the salutary observation that the incidence of HIV infection was too low in both the SAVVY and placebo groups to permit analysis of the microbicide's efficacy.

Adsorption Inhibitors

Adsorption inhibitors block the binding of HIV to target cells. Candidates currently being studied belong to a group of chemicals called polyanions (which include dextran sulfate, proposed as an HIV treatment in the 1980s), which have too high a molecular weight to be absorbed orally. Three adsorption inhibitors are being assessed as microbicides in phase III efficacy trials: PRO 2000 (a naphthalene sulphonate polymer), carageenan (trade name Carraguard, a naturally occurring sulphated sugar polymer), and cellulose sulphate (trade name Ushercell). All three are highly active against both R5 and X4 HIV isolates in vitro and have low toxicity. A small macaque study demonstrated protection against SHIV89.6PD infection in 4/8 animals using PRO2000 (Weber 2001), but there are no published challenge experiments using Carraguard or Ushercell.

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 toxic to viruses like HIV. One such agent, BufferGel (Mayer 2001), is being studied in a phase IIb efficacy trial with PRO2000.

Microbicides: The Next Generation

A number of microbicides that employ direct antiretroviral effects, including several reverse transcriptase inhibitors, are in early-phase human trials. The gel form of the drug tenofovir is currently in phase II trials (alone and in combination with PRO2000) and is moving into expanded phase II testing through the HIV Prevention Trials Network (HPTN). The reverse transcriptase inhibitor UC-781, originally developed by Uniroyal, is in a phase I trial sponsored by BioSyn. The IPM-sponsored dapirivine gel is on a fast track for efficacy evaluation; the organization hopes to move it forward into a phase III trial involving 10,000 women within the next couple of years. On the heels of these compounds are preclinical candidates that target attachment and entry of HIV, such as the CCR5 inhibitors.

Product	Type	Manufacturer	Status
Tenofovir (Viread, TDF)	Nucleotide reverse transcriptase inhibitor	Gilead	Phase II

Preventive Technologies: Pre-Exposure Prophylaxis (PrEP)

PrEP is the acronym for the prophylactic use of antiretroviral drugs to prevent HIV infection. Only one candidate is currently being evaluated as PrEP, the nucleotide reverse transcriptase inhibitor tenofovir (trade name Viread). There are several ongoing and planned trials designed to evaluate both the safety and efficacy of this approach (three sponsored by the US Centers foe Disease Control and two by Family Health International and the Bill & Melinda Gates Foundation). Recent criticisms of these trials led to the suspension of a study site in Cameroon and the termination of a proposed study among sex workers in Cambodia (Mills 2005).

A number of issues were raised by critics, including the long term safety of tenofovir (side effects – albeit rare – include bone loss and kidney damage), the quality of safe sex counseling provided in the studies, provision of clean needles to intravenous drug users in a Thai study, plans for condom provision to participants, and provision of care for participants who seroconvert and/or experience tenofovir-related toxicities. Discussions among the various stakeholders took place over the course of 2005 and, while the issues have not all been resolved, some progress has been made (UNAIDS 2006). Despite these dialogues however, an efficacy trial in Thailand moved ahead in the face of protests about both the process of community consultation and the trial design (Chua 2005).

A new, NIH-sponsored efficacy trial among high-risk Peruvian gay men is slated to start in the near future. Due to promising results seen in the macaque/SIV model cited in the introduction to this chapter, the protocol has recently been amended to switch the study drug from tenofovir alone to the combination tenofovir/emtricitabine pill (Truvada). The CDC-sponsored trial in Botswana has also recently replaced tenofovir with Truvada for the same reason.

Immune-Based Therapies

Immune-based therapies (IBTs) comprise a broad and slightly fuzzy category of treatments that exert their therapeutic effects by acting on the human immune system. IBTs can be loosely subdivided into

therapies that try and boost the immune response to HIV itself (such as therapeutic vaccines), those that might improve immune function overall (e.g. cytokines like IL-2 and IL-7) and slightly futuristic gene therapies that may alter the make-up of the immune system in ways that ameliorate the harmful effects of HIV.

Twenty-five years after the recognition of AIDS as a new immunological disease, there are still no IBTs licensed to treat the condition. To some extent, the surprising degree of immune reconstitution seen in most recipients of antiretroviral therapy (ART) has reduced the sense of urgency that formerly drove the search for immune-based interventions. The persistent mysteries of the human T cell-based immune system have also made it difficult to rationally design therapies that target specific immunological deficits in HIV infection. However, immunology research continues to progress and may yet bear thera-peutic fruit.

Data generated by studies of long term nonprogressors has played a key role in guiding the develop-ment of therapies aimed at bolstering the immune response to HIV. In particular, recent research has delineated a number of HIV-specific T cell functions associated with control of viral replication in the absence of antiretroviral therapy. These functions include the production of IL-2 by CD4 and CD8 T cells, which is also associated with their ability to proliferate in response to HIV antigens (Pantaleo 2004). CD8 T cells capable of performing multiple functions have advantages over those with more lim-ited talents such as the production of interferon gamma alone (Betts 2005). It must be stressed that it is not proven that these types of T–cell responses are responsible for controlling viremia; they may emerge as a consequence of low viral load or they may work alongside other – as yet unknown – fac-tors. 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.

The early termination of the Strategies for the Management of Antiretroviral Therapy (SMART) trial may also have implications for the field of immune-based therapy. The trial investigated the efficacy of intermittent ART in more than 5,000 people with HIV who had been on therapy for an average of six years. Participants were randomized 1:1 to either receive continuous therapy (this was dubbed the viral suppression or VS group) or intermittent therapy (the drug conservation or DC group). For the DC group, the protocol called for interrupting ART when the CD4 count was confirmed to have crested 350 cells/mL and restarting therapy when it fell below 250 cells/mL. Although there was considerable optimism about the prospects for the DC approach, the study was halted in January 2006 due to the DC arm experiencing a risk of disease progression and death double that of par-ticipants in the VS arm. Perhaps surprisingly, there were also slightly more events thought to be associated with drug toxicity (such as cardiac and liver problems) in the DC arm compared to the VS arm.

The results of SMART suggest that some complications normally attributed to drug toxicity, such as cardiovascular disease, may be related – at least in some cases – to the inflammatory response that typically accompanies HIV replication in the absence of ART. One immediate impli-cation of the SMART results is that studies of immune-based therapies that involve ART interrup-tions are being reviewed to ensure that they do not present a risk to participants. In the longer term, the SMART results may buttress the rationale for studying agents that have the potential to reduce inflammation during ART interruptions (such as anti-inflammatory agents and/or therapeu-tic vaccines). Additionally, if the SMART investigators identify any associations between inflamma-tory markers and adverse outcomes in the trial, these markers might prove useful for identifying and evaluating potential IBTs in the future.

Desired Elements of Immune-based Therapies

There are a number of settings where IBTs could potentially prove useful. It is estimated that perhaps

5-10% of recipients experience a discordant response to HAART wherein viral load is successfully suppressed but CD4 T-cell counts do not increase (Carcelain 2001). An IBT that could speed immune reconstitution in such individuals would be highly desirable. An IBT that could delay the need for HAART might reduce both the cost and toxicity of drug therapy, potentially improving quality of life. The same would apply to an IBT that allowed prolonged interruptions of HAART. In this context, the results of the SMART study now argue that additional interventions are needed to render CD4-guided interruptions safe. Additionally, some researchers have proposed using IBTs to specifically target drug-resistant HIV (Stratov 2005). Beyond these potential uses, the desired characteristics of an IBT would be much the same as other therapies: broadly effective, safe, cheap, and convenient.

Therapeutic HIV Vaccines

Product	Type	Manufacturer	Status
ALVAC (vCP1452)	Canarypox vector encoding env, gag, the protease-encoding portion of the pol gene and CTL epitopes from the nef and pol gene products	Aventis Pasteur	Phase II
Lipopeptides	Peptides from Gag, Nef and Pol proteins	Aventis Pasteur/ANRS	Phase II
VRC-HIVDNA009-00-VP	DNA vaccine encoding gag, pol, nef, and multisubtype (A, B, and C) env genes together with an adjuvant gene encoding an IL-2 fusion protein	VRC/NIAID	Phase I/II
VRC-HIVADV014-00-VP	Adenovirus serotype 5 vector containing gag, pol and multisubtype (A, B, and C) env genes	VRC/NIAID	Phase I/II
LC002, a DermaVir Vaccine	DNA expressing all HIV proteins except integrase formulated to a mannosilated particle to target antigen-presenting cells	Research Institute for Genetic & Human Therapy (RIGHT), NIAID/ACTG	Phase I/II
MVA-BN-nef	MVA vector encoding subtype B HIV nef gene	Bavarian Nordic	Phase I
MVA-mBN32	MVA vector encoding multiple CTL epitopes	Bavarian Nordic/Epimmune	Phase I
MRKAd5	Adenovirus serotype 5 vector containing gag, pol and nef genes	Merck	Phase II
Autologous dendritic cells pulsed w/ALVAC (vCP1452)	Canarypox vector encoding env, gag, the protease-encoding portion of the pol gene and CTL epitopes from the nef and pol gene products	ACTG/Aventis	Phase I
Autologous dendritic cell HIV vaccination w/conserved HIV-derived peptides		University of Pittsburgh	Phase I
Multi-epitope DNA	21 CTL epitopes and proprietary, non-HIV derived "universal" CD4 T cell epitope	Epimmune	Phase I
DNA/MVA	DNA vaccine and an MVA vector encoding gag and multiple CTL epitopes	Cobra Pharmaceuticals, Impfstoffwerk Dessau-Tornau GmbH (IDT), Oxford University/MRC	Phase I/II
Remune +/- AmpliVax	Whole-killed subtype A/G recombinant HIV isolate depleted of gp120	Immune Response Corporation	Failed phase III; remains under investigation in context of STIs
Tat vaccine	Recombinant protein	Aventis Pasteur	Phase I
GTU-nef DNA vaccine	DNA encoding the subtype B nef gene	FIT-Biotech	Phase I
TBC-M358 (MVA) TBC-M335 (MVA) TBC-F357 (FPV) TBC-F349 (FPV)	MVA and fowlpox vectors encoding env, gag, tat, rev, nef, and reverse transcriptase genes from HIV-1 subtype B	NIAID, Therion	Phase I
GSK Protein HIV Vaccine	Recombinant Tat, Nef, and gp120 proteins in ASO2A adjuvant	GlaxoSmithKline, Marcus Altfeld, M.D., Ph.D	Phase I
VRC-HIVDNA016-00-VP	Six separate DNA plasmids containing gag, pol, and nef genes from HIV-1 subtype B, and env genes from subtypes A, B, and C	NIH Vaccine Research Center	Phase I
HIV-1gag DNA vaccine IL-15 DNA IL-12 DNA	DNA vaccines encoding HIV-1 subtype B gag, IL-12 and IL-15 (all formulated with bupivacaine)	Wyeth	Phase I
HIV CTL MEP + RC529-SE and GM-CSF adjuvants	DNA vaccine containing CTL epitopes from env or gag	Wyeth	Phase I
GW825780	DNA vaccine encoding a fusion protein incorporating epitopes from RT, Gag and Nef (delivered coated onto gold particles via gene gun)	GlaxoSmithKline	Phase I

The advent of effective antiretroviral therapy led to a resurgence of interest in therapeutic immunization, based on the idea that viral suppression and the attendant immune reconstitution may provide an opportunity to induce new and more effective T-cell responses targeting HIV. The primary goal of therapeutic immunization is to maintain better control of viral replication during ART interruptions, thereby reducing dependence on drug therapy over the long term. At least one trial is also evaluating whether therapeutic immunization early in infection might delay the need for ART. Although these would certainly be desirable outcomes, there are as yet no definitive human data showing they are achievable. Some researchers are optimistic about the prospects for these approaches, while many others remain profoundly skeptical. One common refrain has been that there are no effective precedents for therapeutic vaccines, but, in a limited way, the ALVAC studies cited in the introduction to this chapter may address this concern. The approval of Merck's herpes zoster (shingles) vaccine has also been cited by some researchers as relevant; the vaccine prevents a potential clinical manifestation of herpes zoster in people who are already infected with the varicella zoster virus (VZV) and thus may be considered a therapeutic vaccine.

Because the induction of HIV-specific T cell responses is the current primary goal of both therapeutic and preventive vaccines, many candidates are being studied in both settings. Merck's Ad5 vaccine candidate is being investigated as a therapeutic in two ongoing ACTG trials. One involves the Ad5 vector that encodes only the HIV Gag protein; the goal of the research is to ascertain whether immunization of chronically infected individuals on ART can lead to control of viral replication during a treatment interruption. The other trial involves recently infected individuals and employs the updated Ad5 vector that encodes the HIV Gag, Pol and Nef proteins. This study will also measure the impact of vaccination on viral load when ART is interrupted.

Jonas Salk's Remune is edging its way towards two decades in human trials. Remune underwent a mild renaissance in the HAART era due its one demonstrable talent: its ability to induce HIV-specific CD4 T-cell responses capable of proliferating and producing IL-2 (Maino 2000). Recently initiated trials are also investigating the effects of delivering Remune with a CpG-based adjuvant called AmpliVax (CpG motifs are immune-stimulating stretches of DNA). One of these trials will evaluate the use of Remune alone as a means to delay the initiation of HAART.

Several candidate vaccines have entered therapeutic trials for the first time, including GSK's Nef/Tat/gp120 recombinant protein vaccine, VRC's multi-plasmid DNA vaccine, and Wyeth's DNA vaccines with IL-12 and IL-15 cytokine adjuvants. One of the few new vaccines being studied solely as a therapeutic is Dermavir, a construct containing nearly the entire HIV genome, administered through the skin (Lisziewicz 2006). Dermavir has been shown to induce robust virus-specific T cell responses in macaques, and a phase I study has recently been launched by the ACTG. GSK's most recent therapeutic vaccine candidate, GW825780, has recently undergone phase I testing in uninfected volunteers (Warren 2006) but has not yet been studied in people with HIV. GW825780 is a DNA vaccine (encoding a fusion protein comprising RT, Gag and Nef) delivered using a device called a gene gun or particle mediated epidermal device (PMED). Gene guns work by coating tiny gold particles with the DNA plasmid and then shooting these particles through the skin. One potential problem with gene guns is that they may tend to bias the immune response toward antibody production rather than the cellular immune responses thought to be important in HIV (Weiss 2002).

Cytokine & Immunomodulators

Product	Type	Manufacturer	Status
Interleukin-2 (IL-2)	Cytokine	Chiron	Phase III
Pegasys (peginterferon alfa-2a)	Cytokine	Roche Pharmaceuticals	Phase Ib/II
BAY 50-4798	Modified IL-2	Bayer	Phase I/II
HRG214 Passive Immunotherapy	HIV-specific goat antibodies	Virionyx Corporation Ltd	Phase I/II
Interleukin-7 (IL-7)	Cytokine	Cytheris	Phase I
IL-4/IL-13 trap	Anti-cytokines	Regeneron Pharmaceuticals	Phase I
Serostim	Human growth hormone	Serono	Phase II
Tucaresol	Schiff base forming drug	GlaxoSmithKline	Phase I
MDX-010 anti-CTLA4 antibody	Monoclonal antibody	Medarex	Phase I
Cyclosporine A	Immunosuppressant	Novartis	AIEDRP AIN501/ACTG A5216
Zenapax (daclizumab)	Anti-CD25 monoclonal antibody	National Institutes of Health Clinical Center, Roche Pharmaceuticals	Phase I
Palifermin (recombinant human keratinocyte growth factor)	Fibroblast growth factor	Amgen	Phase I/II (ACTG 5212)
Leukotriene B4 (LTB4)	Neutrophil agonist	Virocell Inc	Phase II
Leflunomide	Pyrimidine synthesis inhibitor	National Institutes of Health Clinical Center	Phase I
VGV-1	Thymus Nuclear Protein extracted from mammalian thymus tissue (TNP-1)	Viral Genetics	Phase II

Gene Therapies

Product	Type	Manufacturer	Status
CD4zeta modified CD4 and CD8 T cells	Ex vivo T cell Modifier	Cell Genesys	Phase II
OZ1 ribozyme gene therapy	Antiviral ribozyme targeted against the tat gene, introduced into CD4 T cells via stem cells	Johnson & Johnson	Phase II
VRX496	Lentiviral vector encoding antiretroviral antisense, introduced into CD4 T cells ex vivo	VIRxSYS	Phase I
HGTV43	Vector encoding antiretroviral antisense, introduced into CD4 T cells ex vivo	Enzo Biochem	Phase II
M87o	Entry inhibitor gene encoded by a lentiviral vector, introduced into CD4 T cells ex vivo	EUFETS AG	Phase I

Interleukin-2

Another category of IBTs comprises candidates intended to improve overall immune function as opposed to just HIV-specific immunity. The hardy perennial of this class of therapies is interleukin-2 (IL-2), which has been in trials since the mid-1980s. IL-2 belongs to a family of chemical messengers called cytokines, which transmit signals among the cells of the immune system. Initially dubbed "T-cell growth factor" due its ability to induce T-cell proliferation, IL-2 is now understood to have more complex effects, including an unexpectedly important role in programmed T-cell death (Waldmann 2001).

Many studies have demonstrated that IL-2, administered either intravenously or subcutaneously, can increase peripheral blood CD4 T cell counts in people with HIV infection (De Paoli 2001). Questions persist, however, about the functionality of these IL-2-induced CD4 T cells. One recent ACTG study found that they did not appear to improve –and may in some cases have diminished–the response to a variety of routine vaccinations such as hepatitis A vaccine (Valdez 2003). The mechanism of IL-2's effect is also uncertain, with recent evidence suggesting it decreases T cell proliferation and increases T cell survival over the long term (Sereti 2004). Side effects such as fever, chills, and malaise are also typically associated with IL-2 administration. Nevertheless, it remains possible that the CD4 T cell increases associated with IL-2 therapy will lead to long-term clinical benefit by delaying HIV-induced CD4 T cell depletion, and this hypothesis is being investigated in two large clinical endpoint trials: SIL-CAAT and ESPRIT. IL-2's manufacturer, Chiron, originally sponsored SILCAAT but pulled its support in 2001, and NIH (already sponsoring the ESPRIT trial) had to step in to prevent the trial's termination. Preliminary results from the two trials should be available in 2005. The impact of IL-2 on CD4 T cell

declines during ART interruptions was investigated in a pilot ACTG study, but the recently published results suggest that it does not delay CD4 T cell loss in this context (Henry 2006). An engineered and potentially less toxic form of IL-2 known as BAY 50-4798 is also under study in a phase I/II trial.

IL-7

IL-7 is a cytokine which plays a key role in T cell development and naïve and memory T cell proliferation and survival (Fry 2005). IL-7 studies in SIV-infected rhesus macaques have shown dramatic increases in peripheral blood CD4 and CD8 T cell counts, without a concomitant increase in SIV replication (Fry 2003; Nugeyre 2003). Although it was originally thought that IL-7 might stimulate thymic production of new T cells, the increases in the macaque studies appeared to result from peripheral naïve and memory T cell proliferation. Results from a recently published phase I trial in eleven individuals with cancer suggest that IL-7 can increase CD4 and CD8 T cell numbers without serious toxicity, at least in the short term (Rosenberg 2006). An ACTG-sponsored phase I trial in HIV infection is ongoing.

Anti-IL-4 and IL-13

Another IBT strategy involves blocking potentially harmful cytokines. A small Biotech company called Regeneron is developing a product called IL-4/IL-13 Trap based on the idea that these cytokines inhibit virus-specific CD8 T cell responses. Results from a phase I dose-ranging trial in HIV-negative volunteers were presented at CROI 2004 showing that the construct was well tolerated with a long half-life of 13 days (Parsey 2004). Further studies in HIV-infected individuals are planned.

Human Growth Hormone

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 and found that thymic mass did indeed increase, and that this was associated with a rebound in naïve T cell numbers (Napolitano 2002). The ACTG is now enrolling a larger study involving over 100 participants that will prospectively evaluate the impact of HGH on thymus size and naïve T-cell reconstitution.

Tucaresol

Tucaresol is a relatively obscure IBT candidate that has languished in GlaxoSmithKline's HIV drug portfolio since the early 1990s. The drug appears to enhance interactions between antigen-presenting cells and T cells and has been shown to boost cell-mediated immune responses both in mice and in humans. Preliminary data from a phase I trial in 17 HIV-infected individuals were presented at the 2004 Retrovirus conference, demonstrating increases in naïve CD4 T-cell counts and the number of T cells containing TRECs (a potential marker for T cells recently produced by the thymus) in the group of participants receiving HAART treatment (Gazzola 2004).

MDX-010, Zenapax

Some experimental IBTs aim to influence T cell function by interacting with signaling molecules on the T-cell surface. One such molecule is CTLA-4, which is upregulated on T–cells in HIV infection and asso-

ciated with the induction of T cell unresponsiveness or anergy (Leng 2002). In June 2003, the Biotech company Medarex launched a phase I trial of an anti-CTLA-4 antibody dubbed MDX-010 in heavily treatment-experienced HIV-infected individuals who were failing HAART, with the aim of blocking the suppressive activity of CTLA-4 and thus improving HIV-specific immunity. Results from this study have not yet been presented and, in response to inquiries, Medarex would only confirm that MDX-010 continues to be evaluated as a potential HIV treatment.

A monoclonal antibody targeting another signaling molecule, CD25 (the IL-2 receptor) is also under evaluation as an HIV therapeutic. Roche manufactures this antibody–approved in 1997 for the prevention of kidney transplant rejection–under the trade name Zenapax (generic name daclizumab). A small phase I trial of Zenapax in HIV infection has recently been completed by the NIH intramural research program with results pending.

Pegylated Alpha Interferon

Straddling the boundary between antiretrovirals and IBTs is the approved hepatitis C treatment, pegylated alpha interferon. Alpha interferon appears to have direct antiviral effects and also enhances cell-mediated immune responses in humans. Though the unpegylated form of alpha interferon was studied for many years as a potential HIV therapy, it was eventually abandoned due to underwhelming results. The newer pegylated form is now once again being studied as an adjunct to ART and in the context of treatment interruptions.

Immunosuppressive Agents

The association between heightened immune activation and HIV disease progression has led some researchers to pursue studies of several drugs typically referred to as "immune suppressants." These drugs include cyclosporine, prednisone, hydroxyurea, and mycophenylate mofetil. All are approved for other indications, and none of the manufacturers are specifically developing these compounds as IBTs. (Bristol-Myers Squibb abandoned studies of hydroxyurea as an anti-HIV IBT in the late 1990s.) Academic researchers nonetheless continue to evaluate their potential, typically as an adjunct to ART or in the context of treatment interruptions. At the time of writing TAG's 2005 pipeline report, it seemed unlikely that any of these agents would receive serious consideration as potential IBTs. But it now appears possible that the results of the SMART study, by suggesting an important pathogenic role for inflammatory processes in HIV infection, may push these approaches back into the spotlight.

A new addition to the ranks of immunosuppressive agents with potential utility in HIV is Arava (leflunomide). Arava is an approved arthritis drug with properties similar to drugs like mycophenylate mofetil and hydroxyurea. Arava inhibits the synthesis of pyramidine nucleotides and may have direct anti-HIV effects (Schlapfer 2003). A phase I study was recently initiated by the NIH intramural program.

CD4 Reinfusion & Gene Therapies

There is a disparate collection of approaches involving infusing CD4 T cells (or in some cases CD34 stem cells) which are first isolated from HIV-infected individuals, then expanded, and in some cases genetically modified in the laboratory, then reinfused as potential IBTs. At least three different biotech companies are attempting to genetically modify CD4 T cells in the lab in order to enhance their resistance to HIV infection, and subsequently reinfusing them into a matched HIV-infected donor. A similar approach modifies both CD4 and CD8 T cells in an attempt to improve their ability to restrict HIV replication. Preliminary results from trials of these approaches have shown some limited promise (Dropulic 2006; Deeks 2002; Amado 2002).

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 (Amado 2004). Enrollment in the phase II OZ1 study was completed in February of 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 is a recombinant form of a naturally occurring human protein, keratinocyte growth factor, manufactured by Amgen. Palifermin is licensed by the FDA to reduce the incidence of severe mucositis (injury to the cells lining the mouth) and to shorten the time with severe mucositis in people receiving cancer chemotherapies. The ACTG is on the cusp of launching a study that will evaluate whether Palifermin can help restore CD4 T cell counts in individuals with a discordant response to HAART (controlled viral load but an inadequate rise in peripheral blood CD4 T cells). The rationale for the trial comes from studies describing a potential role for keratinocyte growth factor in enhancing T cell production by the thymus, via the restoration of the thymic epithelium (Alpdogan 2006).

Leukotriene B4 (LTB4)

LTB4 is a substance produced primarily by neutrophils and activated macrophages. In a phase I safety study in HIV-negative individuals, a group of Canadian researchers noted that the administration of LTB4 can trigger neutrophils to release potent anti-HIV proteins called alpha-defensins (Flamand 2004). As a result, the researchers are now conducting a phase I trial in HIV infection.

VGV-1

VGV-1 is an example of the type of poorly defined, highly dubious immune-based therapy that occasionally makes an appearance in HIV research. HE2000, a DHEA derivative mentioned in last year's pipeline report-but since removed as it is going nowhere–is an archetype of this kind of product. Such therapies tend to have a number of things in common:

- they are supported by little or no published research.
- they are heavily promoted by small companies who torture what little human data they have until it confesses (in other words, they mine insignificant results in the hopes of discovering some significant subgroup result that can be trumpeted in a press release).
- they are researched outside of the U.S. and Europe though the manufacturers are U.S.-based.

In the case of VGV-1, the manufacturer (Viral Genetics, Inc.) has conducted five trials already. Their best spin on the results can be found in an SEC filing online at: http://www.secinfo.com/dRc22.4f8Nn.htm Study sites include Mexico, Bulgaria, China and, most recently, South Africa. The study in China generated considerable controversy due to its shoddy conduct which included failure to properly consent participants. David Cyranoski wrote a news article for Nature about the controversy, noting that "participants interviewed by Nature say they signed informed-consent forms that they could not understand and that doctors made no effort to explain" (Cyranoski 2005). The most recent 137-person, placebo-controlled phase II trial was conducted in South Africa. The results showed no effect on viral load or CD4 T cells counts, yet in their press release, the company celebrates a subgroup analysis that found 14 people in the VGV-1 arm who purportedly showed a

0.5log$_{10}$ drop in viral load at a single timepoint. This is presented as significant because, at the same timepoint, only three placebo recipients had a viral load drop of this magnitude. Viral Genetics is a wholly-owned subsidiary of 5 Starliving Online Inc, which was founded in 1998 "to develop an e-commerce business model designed to service the unique needs of the international affluent consumer."

Conclusion

The next few years promise to be critical for research into biomedical HIV prevention approaches. Data will be forthcoming from efficacy trials of T cell-based vaccines, microbicides and PrEP, and these data will likely define the future direction of these fields. Similarly, important data is likely to emerge regarding immune-based therapies. The clinical impact of IL-2 (if any) will be demonstrated by results from the ESPRIT and SILCAAT trials, while studies of more potent therapeutic vaccines should show whether the hints of efficacy seen with ALVAC were a sign of a brighter future for this controversial approach, or just a teasing mirage. The willingness of J&J to move their gene therapy candidate into an efficacy trial is to be saluted; it is a high-risk endeavor that will undoubtedly move the science forward even if the specific approach does not pan out. TAG will continue to track progress in all of these areas in future pipeline reports.

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On-line Resources

AIDS Clinical Trials Group (ACTG)
http://aactg.s-3.com/

AIDS Treatment Activists Coalition: Vaccines & IBTs
Working Group
http://www.atac-usa.org/default.asp?id=143

AIDS Vaccine Advocacy Coalition
http://www.avac.org/

Alliance for Microbicide Development Microbicide
Research Portal
https://secure.microbicide.org/DesktopDefault.aspx

Community HIV/AIDS Mobilization Project (CHAMP)
(includes extensive resources relating to PrEP)
http://www.champnetwork.org/

European AIDS Treatment Group: New Preventive
Technologies Working Group
http://www.eatg.org/modules.php?op=modload&name=
News&file=index&catid=&topic=19

Global Campaign for Microbicides Pipeline Fact Sheet
http://www.global-
campaign.org/clientfiles/Pipeline_Jan06.pdf

HIVInsite: Clinical Trials Databases and Lists
http://hivinsite.ucsf.edu/InSite?page=li-04-24

HIVInsite/HIV Vaccine Trials Network Pipeline Project
http://chi.ucsf.edu/vaccines/

HIV Vaccine Trials Network
http://www.hvtn.org/

International AIDS Vaccine Initiative: IAVI database of
AIDS vaccines in human trials
http://www.iavireport.org/trialsdb/

International Partnership for Microbicides
http://www.ipm-microbicides.org/

NIH/National Library of Medicine Clinical Trials Database
http://clinicaltrials.gov/

Project Inform's Immune-Based Therapy Information
http://www.projinf.org/indexS.html#immune

Treatment Action Group
http://www.treatmentactiongroup.org

Vaccine Research Center
http://www.niaid.nih.gov/vrc/

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Hepatitis C Virus (HCV) Drug and Vaccine Pipeline 2006

by Tracy Swan

Hepatitis C: Scope of the Problem

Hepatitis C virus (HCV) is a global public health problem. More than 123 million people–2% of the world's population-have evidence of HCV infection, and up to 104 million are chronically infected (Perz 2004). The natural history of hepatitis C is variable. At least 20% of chronically infected persons develop cirrhosis within 20 to 50 years after infection. Once cirrhosis is established, the annual risk for hepatic decompensation is 4.4%, and 1% to 4% of cirrhotics develop hepatocellular carcinoma each year (Di Bisceglie 1997; Hu 1999).

In the United States, an estimated 5 million people have been exposed to HCV, and approximately 3.7 million are chronically infected (Edlin 2005). Hepatitis C-associated liver damage is the leading indication for liver transplantation in the U.S. In 2002, chronic liver disease and cirrhosis were the 12th leading cause of death, 40-60% of which were attributable to hepatitis C (CDC 2001; Kochanek 2004). HCV-related mortality will continue to increase over the coming years as the number of persons who have been infected with hepatitis C for 20 years or more peaks in 2015 (Armstrong 2000). Davis and colleagues have projected a dramatic increase in complications of HCV during the next two decades: the number of cirrhotics and cases of hepatic decompensation will double, the rate of hepatocellular carcinoma will increase by 81%, and liver-related mortality will increase by 180% (Davis 2003).

HIV/HCV Coinfection

Globally, at least four to five million people are coinfected with HIV and hepatitis C (Alter 2006). In the United States, an estimated 30% of HIV-positive persons are coinfected with hepatitis C (Sulkowski 2000). In Europe, overall prevalence of HCV coinfection in the EuroSIDA Cohort is 34% (Rockstroh 2004).

HIV accelerates hepatitis C disease progression, particularly when CD4 cell count is <200/mL (Benhamou 1999; Goedert 2002). HIV coinfection doubles the risk for HCV-associated cirrhosis and increases the risk for hepatic decompensation sixfold. (Graham 2001). HCV coinfection may complicate HIV treatment, since the risk for antiretroviral-associated hepatotoxicity is greater, and discontinuation of anti-HIV therapy occurs more frequently among coinfected persons than in those with HIV alone (Mocroft 2005). Hepatitis C-associated end-stage liver disease has become a leading cause of death among HIV-positive people in the US and Europe (Bica 2001; Salmon-Ceron 2005).

Current HCV Therapy

The current standard for treating hepatitis C involves a 24 to 48 week course of combination therapy, consisting of once-weekly injections of pegylated alpha interferon and daily oral ribavirin. Alpha interferon has antiviral and immunomodulatory properties, and ribavirin's mechanism of action has not been definitively established. The primary objective of HCV treatment is a sustained virological response (SVR), meaning that there is no detectable hepatitis C virus in the blood six months after completion of therapy. SVR is an indication that HCV will remain at undetectable levels for years, and many experts regard it as a cure. Hepatitis C treatment, particularly when it results in SVR, is associated with a reduction in hepatocellular carcinoma among cirrhotic and non-cirrhotic individuals. (Shiratori 2005; Tanaka 2000).

There are significant limitations to efficacy and tolerability of HCV treatment. Only about half of those who complete treatment achieve SVR. Hepatitis C treatment is more toxic and significantly less effective for those with the most urgent need: the HIV/HCV coinfected, persons with advanced liver disease, and liver transplant recipients, in whom HCV is universally recurrent (Carrat 2004; Chung 2004; Kuo 2005; Torriani 2005). Response rates are lower in persons with genotype 1, high baseline hepati-

tis C viral loads (associated with HCV genotype 1 and HIV coinfection), previously treated persons who did not achieve SVR, and African Americans, who comprise the highest-prevalence population in the United States (Blatt 2000; Fishbein 2006; Fried 2002; Jacobson 2005; Pearlman 2006; Shiffman 2006).

Side effects of hepatitis C treatment may be debilitating and some are treatment-limiting. Coinfected people tend to experience more severe side effects, reflected by high discontinuation rates in clinical trials (Cargnel 2005; Carrat 2004). Anemia is a common side effect of ribavirin. Interferon may also induce anemia, neutropenia and thrombocytopenia through bone marrow suppression. Anemia is managed by one of two strategies: reducing the dose of ribavirin, which may compromise treatment efficacy, or by using epoetin alfa, a red blood cell growth factor. Epoetin Alfa use has been associated with improved quality of life during HCV treatment and maintenance of ribavirin dose but has not been directly associated with response to HCV treatment (Afdahl 2004a; Pockros 2004).

Several studies are exploring strategies to optimize HCV treatment outcomes in mono- and coinfection, although none are likely to yield dramatic advances given the drawbacks of pegylated interferon and ribavirin. Trials in treatment naïve persons have focused on shortening the course of therapy, particularly for persons with favorable prognostic factors. For non-responders and coinfected persons, new approaches, such as extending duration of therapy, double-dose pegylated interferon, and high-dose ribavirin are being assessed. In mono-and coinfected persons with advanced liver disease, a maintenance strategy using long-term, low-dose pegylated interferon monotherapy to prevent complications of cirrhosis is being evaluated in several studies. Interim data appear promising, particularly for persons with advanced fibrosis or cirrhosis, portal hypertension and low albumin (Afdahl 2004b).

Studies in the U.S. and parts of Europe have supported the cost-effectiveness of hepatitis C treatment, although it remains prohibitively expensive for the majority of infected persons worldwide (Sheperd 2004; Siebert 2003; Sullivan 2004). A 48-week course of HCV treatment costs at least $20,000 USD (Saloman 2003). Clinician time, laboratory monitoring, and therapies used to manage hematological and neuropsychiatric side effects significantly increase the expense of treatment.

Desirable Elements for Future Therapies

Novel therapies for hepatitis C must be less toxic and more effective than the current standard of care. New HCV antiviral drugs must be potent and present a high genetic barrier to the development of resistance. Ideally, HCV treatment will rapidly drive down HCV RNA to undetectable levels, while stimulating robust immune responses to keep the virus at bay. Any new add-on therapy to pegylated interferon and/or ribavirin should significantly increase efficacy and shorten treatment duration without adding toxicity. Therapeutic progress may be near with the advent of the following approaches:

- Effective first-line therapies for "hard-to-treat "populations:
    - HIV/HCV coinfected persons
    - African Americans
    - persons with genotype 1 and/or high baseline HCV RNA
    - transplant recipients
    - people with advanced liver damage
- Better second-line treatments for relapsers and non-responders
- Therapies to reverse or halt fibrosis progression and decrease liver inflammation
- Oral therapies that could eliminate injection site reactions and patient discomfort with self-injection
- Affordable treatments, accessible to all who require them, since hepatitis C is often a disease of poverty

The Clinical Pipeline

Get Down and Stay Down: Antiviral Agents

> The rate of HCV production…is larger than the current estimates for viral production in HIV-infected individuals .The large viral production rate…implies that mutations that make the virus more fit under treatment could be rapidly produced. Indeed, it was found that failure of IFN treatment is associated with large quasi-species diversity and high viral load… Thus, as for HIV, initially treating HCV aggressively should be considered as a means of increasing the success of therapy. -A.U. Neumann (Science 1998)

Hopefully, the therapeutic paradigm for hepatitis C will shift toward less toxic, more effective and shorter course treatment in the coming years. New drugs specifically targeting the hepatitis C virus are currently in clinical trials. Oral polymerase and protease inhibitors are being studied in combination with pegylated interferon, with or without ribavirin. As with HIV, multi-drug regimens will be necessary to prevent resistance. Interferon will likely continue as the therapeutic backbone of HCV therapy until enough new drugs exist to construct effective multi-agent regimens.

Hepatitis C Protease Inhibitors (oral)		
Product	Manufacturer	Status
GS 9132/ACH 806	Gilead Sciences/Achilion	Phase I
SCH 503034	Schering Plough	Phase II
VX-950	Vertex/ Tibotec	Phase II

Hepatitis C Protease Inhibitors

The HCV protease enzyme is a difficult–but important–target for anti-HCV therapy, described as "greasy" by researchers. The hepatitis C NS3/4A protease is involved with viral replication and interferes with host immune responses to hepatitis C. Recent research suggests that the NS3/4A protease disrupts signaling pathways responsible for inducing endogenous interferon, thus allowing HCV to elude one of the host's innate immune responses. Inhibiting the NS3/4A protease may increase treatment efficacy by augmenting or restoring host interferon responsiveness (Foy 2003; Lemon 2005; Li 2005). Although targeting HCV protease may have a dual therapeutic benefit, what matters most is whether this class of drugs will be potent enough to drive down hepatitis C viral load before resistance develops.

Boehringer Ingleheim's BILN-2061 was the first HCV protease inhibitor to enter clinical trials. Although it established proof-of-concept, BILN-2061 was discontinued due to cardiac toxicity in animal studies (Hinrichsen 2004; Lamarre 2003). Luckily, three other HCV protease inhibitors have entered human trials without reports of serious toxicity, and other candidates are in pre-clinical development. Gilead and Achillion are currently studying their HCV protease inhibitor in healthy volunteers and they plan to initiate brief studies in people with HCV later this year.

HCV protease inhibitors from Vertex (VX-950) and Schering (SCH 503034)–both active against the difficult-to-treat hepatitis C genotype 1–have moved into Phase II studies. Both candidates have been granted Fast Track designation by FDA. Fast tracking allows expedited development and review of agents that may address unmet needs, particularly for serious or life-threatening conditions (http://www. fda.gov/ CbER/inside/fastrk.htm).

Data from 14-day Phase I studies of these HCV protease inhibitors, were promising. Each was studied as monotherapy, and in combination with pegylated interferon (vs. pegylated interferon monotherapy).

Vertex has conducted a 28-day study of VX-950 with pegylated interferon plus ribavirin (see Table 1: Phase I Studies of SCH 503034 and VX-950). Although the trial strategies are similar, the study populations differ. SCH 503034 has been evaluated in non-responders, while VX-950 has been studied in treatment-naïve persons.

Table 1. Phase I Studies of SCH 503034 and VX-950				
Agent(s)	Population	Duration	Dosing	HCV RNA Response
SCH 503034	N=12; HCV genotype 1; non-responders to prior peg-ifn + rbv	14 days	400 mg/tid	Mean maximum reduction: 2.06 log10 (range: 1.1-2.07)
SCH 503034 + Peg-IFN alfa 2b	N=12; HCV genotype 1; non-responders to prior peg-ifn + rbv	14 days	400mg/tid; plus Peg-IFN1.5µg/kg once weekly	Mean maximum reduction: 2.9 log10 (range: 2.3-4.1)
Peg-IFN alfa 2b	HCV genotype 1; non-responders to prior peg-ifn + rbv	14 days	1.5µg/kg once weekly	Mean maximum reduction: 1.1 log10
SCH 503034 + Peg-IFN	N=10; HCV genotype 1; non-responders to prior peg-ifn +/- rbv	14 days (as part of a crossover study with 3 treatment arms)	400mg/tid; plus Peg-IFN1.5µg/kg once weekly	4/10 had undetectable HCV RNA within two weeks of treatment
Vertex 950	N=8; HCV genotype 1; treatment-naïve	14 days	750 mg/q 8 hours	Median reduction: 4.0 log10
Vertex 950 + Peg-IFN	N=8; HCV genotype 1; treatment-naïve	14 days	750 mg/q 8 hours; plus Peg-IFN alfa-2a 180µg/week	Median reduction: 5.5 log10
Peg-IFN	N=4; HCV genotype 1; treatment-naïve	14 days	Peg-IFN alfa-2a 180µg/week	Median reduction: 1.0 log10
Vertex 950 + Peg-IFN and ribavirin	N=12; HCV genotype 1; treatment-naïve	28 days	750 mg/q 8 hours plus Peg-IFN alfa-2a 180µg/week and ribavirin (1000-1200 mg/day)	All participants had undetectable (<10 copies/IU/mL) HCV RNA by day 28; the higher the baseline HCV RNA, the longer it took to achieve undetectable HCV RNA

Schering is conducting a Phase II, placebo-controlled, dose-finding study of SCH 503034 in non-responders with HCV genotype 1. Originally, three doses (100, 200, or 400 mg) TID-of SCH 503034 (or placebo) were evaluated, with background therapy of pegylated interferon, with or without ribavirin. The duration of treatment ranged from 24 to 49 weeks. Schering did not initially allow African Americans into the study, drawing sharp criticism from advocates. The protocol was amended to add an additional 65-person arm, studying a doubled dose (800mg/TID) of SCH 503034. Schering permitted 15 African Americans to enroll in the high-dose arm, an intervention unlikely to yield meaningful safety and efficacy data in this population. The initial exclusion of African Americans–the highest-prevalence population in the Untied States-was scientifically and ethically unjustified.

The mid-stream dose-doubling in the Phase II study of SCH 503034 signaled potential problems with drug potency; indeed, the independent data safety and monitoring board (DSMB) was concerned about non-responders in the 100, 200, and 400 mg arms (all of whom discontinued treatment as per protocol). The DSMB recommended that virological responders be given the 800 mg dose plus ribavirin; Schering and FDA concurred, and the study continues.

Vertex's Phase II program is being conducted in treatment–naïve individuals with HCV genotype 1. PROVE 1 and PROVE 2 are trials evaluating a 750mg/TID dose of VX 950 plus pegylated interferon, with or without ribavirin: Duration of treatment ranges from 12 to 48 weeks. Vertex will initiate a study of VX-950 in non-responders in mid-to-late 2006.

Dosing, Boosting and Resistance

SCH 503034 and VX-950 are taken three times daily (TID), a regimen presenting adherence challenges which could increase the risk for developing resistance. Regimens with less-frequent daily dosing are associated with better adherence in HIV (Stone 2001). Pharmacokinetic boosting using ritonavir, a powerful metabolic inhibitor marketed by Abbott Laboratories, has been a successful approach for reducing pill burden and dosing frequency of HIV protease inhibitors. An Abbott-sponsored study reported that ritonavir significantly increased plasma concentrations of SCH 503034 and VX-950 in rats (Kempf 2006). Vertex is planning a multi-dose, drug-drug interaction study of ritonavir and VX-950 in mid-to-late 2006. Schering has not announced plans to study ritonavir boosting. Unfortunately, ritonavir is expensive, and manufacturers developing drugs that depend on it for boosting must pay a royalty to Abbott. As a result, companies developing HCV protease inhibitors may be reluctant to use ritonavir because of the financial impact.

Hepatitis C replicates rapidly, making billions of copies per day. Inevitably, mutations occur. Some may confer resistance to HCV-specific antiviral drugs. HCV protease inhibitors will have to be sufficiently potent to quickly eliminate viral load before resistance can develop. Mutations associated with resistance to single or multiple HCV protease inhibitors have been characterized (Lin 2005). It is unclear whether these mutations were present prior to HCV treatment or if they emerged during treatment. During 14 days of VX-950 monotherapy, four of eight study volunteers experienced a plateau or viral rebound, but no viral breakthroughs occurred in the VX-950 plus pegylated interferon group (Reesink 2006). Although low-level resistance has been detected in persons who experienced virological breakthrough during 14 days of treatment with VX-950, Vertex claims that the replicative fitness of resistant virus is significantly impaired (Kieffer 2006).

Conjecture about baseline vs. emergent HCV drug resistance merits further investigation, particularly in coinfected people, who usually have higher HCV RNA levels than those with hepatitis C alone. Bagaglio and colleagues reported mutations in the NS3 domain of hepatitis C, some of which conferred resistance to VX-950, in a pilot study of 25 coinfected people. Overall, HCV genotype 1 was associated with more mutations than HCV genotype 3a (means of 10 vs. 5). Resistance-conferring mutations on the binding site of the HCV protease were identified in two coinfected persons with HCV genotype 1; both were taking an HIV protease inhibitor (Bagaglio 2006). These data support larger studies to assess prevalence of resistance to HCV protease inhibitors in coinfected people.

Hepatitis C Polymerase Inhibitors

Hepatitis C Polymerase Inhibitors (oral)		
Product	Manufacturer	Status
HCV-796	ViroPharma/Wyeth	Phase Ib
NM283 (Valopicitabine)	Idenix	Phase II
R1626	Roche	Phase I
XTL 2125	XTL Biopharmaceuticals	Phase I

Several nucleoside and non-nucleoside analog HCV polymerase inhibitors are in preclinical development, and four agents are in human trials. Some are expected to be effective across HCV genotypes. As with the HCV protease inhibitors, the threat of resistance looms large; mutations conferring resistance to HCV polymerase inhibitors have already been identified (Mo 2005).
HCV-796, a non-nucleoside analog, is active against multiple HCV genotypes. In a 14-day dose-ranging

study in treatment–naïve persons, drug exposure reached a plateau at 1000 mg/day. At all doses, the decrease in HCV RNA peaked at day four; thereafter, HCV RNA crept back up, possibly due to resistance, which is currently being evaluated. No serious adverse events were reported (Villano 2006). Safety and activity of HCV-796 plus pegylated interferon are being evaluated in a phase Ib trial.

Furthest along is valopicitabine, a nucleoside analog HCV polymerase inhibitor. Valopicitabine is being evaluated in two ongoing phase II trials, one in non-responders and one in treatment-naive persons with HCV genotype 1. The non-responder trial was evaluating safety and efficacy of valopicitabine (400 mg, 400 mg ramping up to 800 mg, and 800mg) plus pegylated interferon vs. pegylated interferon plus ribavirin. In the treatment naïve trial, valopicitabine dosing ranged from 200 mg to 800 mg. Due to gastrointestinal intolerance, particularly in the treatment naïve study, both protocols have been amended to allow a maximum dose of 400 mg/day. In the non-responder study, at week 24, HCV RNA decreased by >2 log10 in all dosing arms; the greatest decrease (3.29 log_{10}) occurred in the 800 mg arm. At week 8 in the treatment-naïve trial, the greatest decrease in HCV RNA (4.50 log_{10}) occurred in the 800 mg arm. (Afdahl 2006; Dieterich 2006).

The implications of the valopicitabine dose reduction are unclear, since virological responses in both studies were dose-dependent. An interaction study with ribavirin is planned, and the phase III program will evaluate valopicitabine plus pegylated interferon vs. valopicitabine plus pegylated interferon and ribavirin (pending results from the interaction study).

Safety, pharamcokinetics, and pharmacodynamics of multiple, ascending doses of R1626, a prodrug of the nucleoside analog R1479, are being evaluated in an ongoing study of treatment-naïve persons with HCV genotype 1. So far, no serious adverse events have been reported (Roberts 2006). R1626 is slated to enter phase II by the third quarter of 2006.

XTL announced commencement of a Phase I study of XTL 2125 in May 2006.

Hepatitis C Alpha-Glucosidase Inhibitors

Alpha-glucosidase inhibitors prevent the removal of glucose residue necessary for assembly of HCV virions. A phase IIb study is looking at safety and efficacy of MX-3253 (celgosivir) and pegylated interferon, with or without ribavirin, in non-responders with HCV genotype 1. Migenix, the sponsor, is also conducting a 12–week viral kinetics study, evaluating the activity of celgosivir and pegylated interferon, with or without ribavirin, in non-responders with HCV genotype 1. Results are expected at the end of 2006 or in early 2007. An additional phase II study of safety, tolerability, anti-viral activity and pharmacokinetics of celgosivir and pegylated interferon with or without ribavirin in treatment naïve persons, is expected to open in mid-2006.

Immunomodulators

The development of therapies to stimulate and/or augment host immune responses to HCV is an exciting prospect, although these therapies may be less effective in immunosuppressed persons. Clearly, once proof-of-concept has been established in persons with HCV, trials in coinfected persons should be stratified by CD4 cell count.

Toll-like Receptor Agonists

Toll-like Receptor Agonists (oral)		
Product	Manufacturer	Status
ANA-975	Anadys/Novartis	Phase I: Suspended
Actilon™ (CPG 10101)	Coley Pharmaceuticals	Phase II

Toll-like receptors (TLRs) recognize specific pathogens by the patterns on their surfaces. TLRs bind to molecular signals on select invading pathogens, thus signaling the immune system. TLR signaling triggers a cascade of responses, activating innate and adaptive immunity. Toll-like receptor agonists bind to TLRs and stimulate immune responses. So far, ten toll-like receptors have been identified, and two are being studied as a treatment for HCV: ANA975, a TLR–7 agonist, and Actilon™, a TLR 9 agonist.

Stimulating immune response is a promising approach for HCV therapy, but TLR agonists may be less effective for HIV-positive persons. HIV-associated chronic immune activation may be associated with diminished upregulation and responsiveness of TLR-9, which may contribute to impaired immune responses (Ayash-Rashkovsky 2005).

Isatoribine is a nucleoside analog TLR-7 agonist delivered by subcutaneous infusion. A phase I study of isatoribine has been conducted in 32 volunteers with chronic hepatitis C. In this seven-day study, antiviral responses were dose-dependent, reaching >1 $\log_{10}$ in four of twelve persons in the highest dose group. Virological response was associated with induction of an anti-HCV immune response during treatment. Isatoribine was generally well tolerated; adverse events were mild to moderate (Horsmans 2005). This initial proof-of concept study was followed by the development of ANA 975, an oral prodrug of isatoribine. Unfortunately, development of ANA 975 has been suspended, pending evaluation of animal toxicity data.

Actilion (CPG 10101) is a TLR-9 agonist. Currently in phase II, it has been granted Fast Track designation by FDA. Early virological response data from an ongoing Phase Ib study in previously treated relapsers with HCV genotype 1 indicate antiviral efficacy of CPG 10101, particularly in combination with pegylated interferon and ribavirin (McHutchison 2006).   A three-arm, ongoing phase II study is evaluating two doses of CPG 10101 with peg-interferon and ribavirin in 90 previously treated persons with HCV genotype 1. Week twelve data are expected at the end of 2006.

New Formulations and Types of Interferon

Interferons (Injectable)		
Product	Manufacturer	Status
Albuferon	Human Genome Sciences/Novartis	Phase II
BLX-883 Locteron-interferon	Biolex Therapeutics/OctoPlus	Phase I
Consensus Interferon; Infergen	Valeant	Phase III

There is a pressing need to develop forms of interferon that are more effective, less toxic, and more convenient than pegylated interferon, the current standard of care.

Albuferon is interferon alfa-2b that has been fused to human albumin to provide continuous, multi-week exposure from a single infusion as the molecule is slowly released from the albumin. An ongoing Phase II study in 458 treatment–naïve persons with HCV genotype 1 is evaluating different doses and dosing schedules of albuferon plus ribavirin (versus pegylated interferon plus ribavirin). At week 12, the best results have been reported with 1200µg of albuferon every 14 days (87.5% had early virological response, vs. 85.7% in the pegylated interferon arm, 80.4% in the 900µg arm, and, disappointingly, 73.4% of the once-monthly 1200µg arm). There was no significant difference in serious adverse events by study arm (Zeuzem 2006). Higher albuferon doses (1500µg and 1800µg every 14 days) are being evaluated in non-responders; so far, safety seems equivalent to that of lower doses (Rustgi 2006).

Locteron-interferon is a continuously-released formulation of interferon alfa-2b. Phase I pharmacokinetic and pharmacodynamic data from healthy volunteers support dosing every 14 days (Bechet 2006). A phase II study will be initiated in during mid-to-late 2006.

Although two studies have supported use of daily infergen in mono-and coinfected non-responders, current labeling supports thrice-weekly dosing in non-responders (Cornberg 2006;Leevey 2005). An ongoing Phase III study, the DIRECT trial, was designed to create labeling for daily dosing. Results are expected in 2007. Infergen is also being studied in treatment-naïve persons with HCV genotype 1.

Mono-and Polyclonal Antibodies

HCV is universally recurrent after liver transplantation. Prophylaxis with hepatitis B immunoglobulin has been a successful approach for preventing recurrent hepatitis B infections in liver transplant recipients, so a prophylactic strategy may also be effective for hepatitis C (Vargas 2002). Thus, hepatitis C immune globulins have been developed.

Mono-and Polyclonal Antibodies (subcutaneous or intravenous infusion)		
Product	Manufacturer	Status
Bavituximab (Tarvicin)	Peregrine Pharmaceuticals	Phase I
Civacir	Nabi Biopharamceuticals	Phase I/II
XTL-6865	XTL Bio	Phase I

Bavituximab is a monoclonal antibody that, according to the sponsor, will bind to aminophospholipids on the exterior of cells that are either malignant or have been infected by a virus. It is currently in a phase I study of non-responders and relapsers to pegylated interferon plus ribavirin.

Civacir is a polyclonal antibody made from human plasma and purified hepatitis C antibodies. After a FDA study of safety and pharmacokinetics in 18 HCV-infected liver transplant recipients, Civacir received Fast Track designation and Orphan Drug Status. Orphan Drug Status may be granted to products for conditions that affect less than 200,000 people in the US. Orphan Drug Status has many benefits for the sponsor: tax incentives, financial and technical support for clinical trials, an exclusive market for seven years, and waived FDA user fees. A phase II proof-of-concept study in HCV-infected liver transplant recipients is slated for mid-to-late 2006. Results are expected in mid-2008.

XTL-6865 is comprised of two monoclonal antibodies, Ab68 and Ab65. This combination replaced HepeX-C, a single Ab68 monoclonal antibody candidate. HepeX-C has been evaluated in a dose-ranging study and in HCV-infected transplant recipients in whom antiviral activity was established. A phase I study in people with chronic HCV is ongoing.

Preventive and Therapeutic Vaccines

The scientific basis for vaccine development comes from observation of the natural history of hepatitis C. The virus can be spontaneously cleared, usually within a few months after infection. Spontaneous viral clearance is achieved by 15-55% of acutely infected persons and is linked to HCV-specific immune responses (Aberle 2006; Gerlach 2003). Persons who have achieved spontaneous viral clearance are more likely to do so again upon re-exposure to hepatitis C, demonstrating protective immunity (Mehta 2002). Several preventive and therapeutic vaccine candidates aiming to stimulate humoral and cellular immune responses to hepatitis C have moved into clinical development.

GI-5005 is a yeast-based vector that expresses hepatitis C NS3 and core proteins. It is intended to be taken up by antigen-presenting cells and elicit an immune response that will clear HCV-infected cells. It is expected to be effective against all HCV genotypes. GI-5005 is being evaluated in a phase Ib study in partial responders, relapsers, and treatment naïve persons with chronic hepatitis C.

Nevens and colleagues established proof-of-concept for a therapeutic recombinant E1 HCV vaccine. They were able to increase cellular and humoral immune responses to HCV in chronically infected persons, and some (9/24) experienced histological improvement after multiple vaccinations over a 65-week interval (Nevens 2003).

Hepatitis C Vaccines		
Therapeutic Vaccines		
Product	**Manufacturer**	**Status**
GI-5005	Globe Immune	Phase Ib
gpE1glycoprotein with alum adjuvant	Innogenetics	Phase I/II
IC-41 cocktail of synthetic peptides with adjuvant	Intercell	Phase II
gpE1/gpE2 proteins with oil/water adjuvant	Chiron/ Novartis	Phase Ib
NS3, NS4, NS5-C polyprotein with ISCOMATRIX® adjuvant	Chiron/CSL/Novartis	Phase Ib
Preventive Vaccines		
Product	**Manufacturer**	**Status**
Recombinant gpE1/gpE2 with oil/water adjuvants	Chiron/Novartis	Phase I
Recombinant gpE1 in alum	Innogenetics	Phase I/II

Since HCV progresses slowly, assessing the effect of therapeutic vaccination on liver histology may be a lengthy process. In fact, Innogenetics has extended the duration of an ongoing, placebo-controlled phase II study because an earlier trial indicated that fibrosis progression in the placebo group was slower than expected. IC-41 is expected to enter phase III in 2008.

There is evidence for a preventive hepatitis C vaccine in chimpanzees. Folgori and colleagues reported that a vaccine made from DNA coding of the hepatitis C nonstructural region elicited cellular immune responses that prevented chimpanzees with acute HCV from developing chronic infections (Folgari 2006).
Chiron has developed a vaccine made from hepatitis C envelope glycoproteins that is currently in phase I. In earlier trials, Chiron's HCV vaccine candidate prevented chronic HCV infection via cellular and humoral immune responses in a majority of chimpanzees challenged with a homologous virus (Houghton 2005; Abrignani). Chiron is hoping to have a preventive vaccine candidate approved by 2010.

Anti-Fibrotic Agents

A therapeutic approach focusing on improving the condition of the liver–or at least stabilizing fibrosis progression–is sensible, given the high rates of virological non-response to current therapies. Given the natural history of HCV, which has been described as "indolent," it may be difficult to assess the efficacy of these agents expeditiously, or without multiple biopsies.

Anti-Fibrotic Agents (oral)		
Product	**Manufacturer**	**Status**
GI262570	GlaxoSmithKline	Phase II
IDN 6656 (oral) Caspase Inhibitor	Idun Pharmaceuticals/Pfizer	Phase II

GI262570 is a peroxisome proliferator-activated receptor (PPAR) gamma agonist, from the same family as rosiglitazone and pioglitazone. PPARs have several functions, including regulating transcription of genes involved in metabolism of glucose, lipids and cholesterol, and controlling inflammatory responses in the liver and other areas of the body. Hopefully, GI262570 will decrease inflammation and liver cell death. An ongoing phase II study is evaluating anti-fibrotic activity of GI262570 in persons who

could not tolerate or respond to HCV treatment.

IDN 6656 is a caspase inhibitor with anti-apoptotic activity. It was granted Orphan Drug designation for use following liver transplantation. A phase II study of IDN 6656 in non-responders is no longer enrolling.

Good News, Bad News: More Tolerable, Not As Effective

Zadaxin–Zadaxin, an injectable immunomodulator made from synthesized human thymus extract, is unlikely to be developed as an HCV therapy. In a U.S. phase III study, adding Zadaxin to pegylated interferon did not increase sustained virological response rates among cirrhotic non-responders. SciClone's European partner, Sigma-Tau, is sponsoring a Phase III study combining Zadaxin with pegylated interferon and ribavirin; results are expected in 2008. If results are favorable, data from an additional trial confirming that Zadaxin use is associated with a significant increase in SVR rates will be necessary for approval.

Viramidine–Viramidine is a ribavirin prodrug that targets the liver. Viramidine does not penetrate red blood cells as efficiently as ribavirin and is thus associated with lower anemia rates. Unfortunately, viramidine is also less effective than ribavirin. Viramidine failed to demonstrate non-inferiority in VISER 1, a phase III trial conducted by the sponsor. By intent-to-treat analysis, overall SVR was 38% in the pegylated interferon plus viramidine arm vs. 52% in the pegylated interferon plus ribavirin arm. A post-hoc analysis suggests that weight-based dosing might be more effective, although the incidence of anemia increased with higher viramidine exposure (4% for <18mg/kg vs. 12.5% for >23 mg/kg). (Benhamou 2006) Regrettably, a second phase III trial, VISER 2, is using the same dosing schema as did VISER 1. Results are expected in late 2006 or early 2007. The sponsor, Valeant Pharmaceuticals, is hoping to get the drug approved without doing a prospective study of the safety and efficacy of weight-based viramidine. A less toxic replacement for ribavirin is highly desirable but not if it is less effective. Safety and efficacy of weight-based viramidine must be studied prospectively before approval.

Odds & Ends: Floor Wax, Dessert Topping and… an HCV Therapy?

It is difficult to predict which agents are promising and which are simply clogging the pipeline.

Other Interferons		
Product	**Manufacturer**	**Status**
Multiferon	Viragen	Phase III
Omega Interferon (Duros®)	Intarcia Therapeutics	Phase I/II
Oral Interferon	Amarillo Biosciences	Phase I

Multiferon is being studied in non–responders at sites in Greece and Mexico. It has been approved to treat melanoma in Sweden.

Intarcia Therapeutics is developing an implant designed to deliver a continuous, three-month supply of omega interferon (another Intarcia product). The Duros® implant has not yet entered human trials, and omega interferon is being studied in a series of Russian trials. A phase II study is evaluating safety, efficacy and tolerability of daily injections of omega interferon as a surrogate for Duros® delivery, with or without ribavirin, in treatment naïve persons with HCV genotype 1. Results are expected at the end of 2006.

Low-dose oral interferon, while exciting in theory, does not seem to be sailing forward in hepatitis C, although the sponsor is evaluating it as treatment for oral warts and to prevent influenza and respiratory infections.

Other Antiviral drugs (oral)		
Product	**Manufacturer**	**Status**
Suvus (Virostat /BIVN-401)	Bioenvision	Phase II
Alinia® nitazoxanide	Romark Laboratories	Phase II

Suvus, formerly known as Virostat, is currently in Phase II. A non-responder trial in persons with HCV genotype 4 is ongoing in Egypt, as are investigator-initiated studies in Europe.

Alinia (nitazoxanide) is from a class of drugs called thiazolides. Alinia was originally developed for activity against intestinal parasites and anaerobic bacteria. In cell cultures, nitazoxanide demonstrated activity against hepatitis B and hepatitis C via inhibition of viral protein synthesis. So far, the drug has been studied as monotherapy in persons with HCV genotype 4, including non-responders to previous therapy. After 24 weeks of treatment, 20 study participants in the Alinia arm had undetectable HCV RNA vs. none of those in the placebo arm. No serious adverse events have been reported. Participants are currently being followed off-treatment. Other ongoing Phase II studies are evaluating Alinia® plus pegylated interferon. Results are expected in late 2006.

Interferon Enhancer?

EMZ-702 has been described as an interferon enhancer, although the mechanism of action has not been detailed. A phase I study is evaluating the safety, tolerability, activity and pharmacokinetic profile of EMZ-702 infusions, in combination with pegylated interferon plus ribavirin in non-responders with HCV genotype 1.

IRES Inhibitor–Safety and activity of mifepristone, also known as VGX-410 or RU-486, are being evaluated in a phase II study. Mifepristone is an oral internal ribosomal entry site (IRES) inhibitor, expected to have activity against all HCV genotypes. Results are expected in 2007.

Antisense–AVIBio Pharma is developing an injectable antisense drug, currently in phase I/II. AVI-4065 is being studied in both treatment naïve persons and non-responders to standard interferon plus ribavirin.

Research & Policy Issues

Currently, the hepatitis C treatment scenario resembles pre-HAART era HIV: a suboptimal standard of care, with a pipeline full of promising agents. Interferon-free, multi-drug regimens are years away. New drugs may increase efficacy of interferon-based regimens and shorten treatment duration, but they will not eliminate interferon-associated toxicities. A growing population of non-responders will need second-line therapies. As with HIV, simple adding one new drug to a previously unsuccessful treatment regimen is unlikely to produce durable results.

We need more than new drugs. Well-designed clinical trials can define standard of care. As more therapeutic options become available, treatment strategy trials must be performed. Industry-sponsored registration trials will not provide adequate data, since hard-to-treat, high prevalence populations are often excluded, and companies are too often unwilling to participate in multi-experimental agent trials. Without public and private sector research partnerships, Roche and Schering–who market pegylated interferon and ribavirin respectively–may effectively determine a research agenda anchored to their products, even though evolving therapeutic opportunities and challenges call for innovative strategies.

Several research issues warrant consideration from regulators and the community:

(**1.**) Sponsors must study safety, efficacy and tolerability of new HCV treatments/regimens in clinically relevant populations prior to gaining approval:

- FDA should require studies of novel HCV therapies in HIV/HCV coinfected persons as a pre-requisite for approval. As soon as possible, sponsors must conduct pharmacokinetic and drug-drug interaction studies to facilitate HCV treatment trials in coinfected people.
- Evaluate novel agents and regimens in people with urgent need. New therapies should be promptly evaluated in cirrhotics, and, when safety data supports further investigation, in transplant candidates and recipients prior to approval—and made available through expanded access programs.
- Candidates should be studied in a diverse population as early as possible—at least by Phase II-to detect signals of potential variations in pharmacokinetic or pharmacodynamic parameters (including dosing and tolerability), safety and efficacy.
- Sponsors must commit to enroll in registration trials a sufficient number of African Americans for subgroup analysis of safety, efficacy and tolerability.
- Former and current drug users should no longer be excluded from clinical trials on the basis of drug use alone.
- HCV treatment trials should not exclude persons with a psychiatric history. Instead, study volunteers should undergo a baseline psychiatric assessment and ongoing counseling and psychiatric care, as indicated by regular assessment of neuropsychiatric side effects during treatment.

(**2.**) Assay standardization: During treatment trials and follow-up, HCV RNA should always be measured using the most sensitive assay. Trial participants should receive these results in real time. The threshold of detection should be included in all publications and presentations.

(**3.**) Length of follow-up: Current parameters for response to treatment may not apply to new therapies, the duration of virological and histological follow-up may need to be extended. Archived, drug-resistant virus might emerge from reservoirs. Low levels of HCV RNA have been detected in persons who have achieved spontaneous viral clearance and sustained virological response. Although the clinical significance of persistent, low-level HCV viremia is unclear, longer-term post-treatment viral load monitoring should be considered, particularly for immunocompromised persons. The durability of treatment-associated histological benefit is unclear, because post-treatment biopsies are usually performed within 18 months after completion of therapy. Post-treatment follow-up should be lengthened, particularly for new drugs that may have unanticipated effects on liver histology. Novel therapies designed to improve liver histology–rather than eliminate the virus–require a different duration of follow-up.

(**4.**) Vaccine-related endpoints: Correlates of immunity for preventive vaccines need to be established. Immunogenicity should be characterized in HIV-positive people. The duration of vaccine-induced immunity needs to be characterized by long-term follow-up of vaccine trial volunteers.

(**5.**) Resistance characterization and assay development: Resistance mutations to HCV protease and polymerase inhibitors have already been identified. Resistance assays need to be developed and their use standardized across clinical trials.

(**6.**) Definition of study populations: "Non-responders" is a broad category that may include relapsers and people who experienced virological breakthrough during HCV treatment. The likelihood of SVR from re-treatment depends on the initial response and the original treatment regimen. If either dose or duration of the initial therapy was insufficient, achieving SVR upon re-treatment may depend on adequate dosing and duration, and a regimen with superior efficacy may not be required. Study popula-

tions must be strictly defined to properly assess efficacy of re-treatment regimens and new agents, and to allow for comparison of results from re-treatment trials.

(**7.**) Genotype-specific treatment strategies: The current candidate HCV protease inhibitors target HCV genotype 1. Although the current standard of care is more effective in people with HCV genotypes 2 and 3, it leaves much to be desired in terms of toxicity and tolerability. Novel agents and treatment strategies also need to be developed and evaluated in persons with non–HCV 1 genotypes.

(**8.**) Validation of non-invasive serum markers: Whenever possible, pre-and post-treatment assessment of liver histology should include liver biopsy and a serum biomarker panel. Hopefully, this will lead to validation of non-invasive testing to eventually replace biopsy.

Guide me!

Treatment guidelines translate research results into clinical practice and avert therapeutic chaos by responding to an evolving standard of care. Currently, hepatitis C treatment guidelines are produced by the American Association for the Study of Liver Diseases (AASLD), the Veteran's Administration (VA) and through National Institutes of Health (NIH) Consensus Development Conferences, the European Association for the Study of Liver Diseases (EASL), and others (see Resources, at the end of this section). These assorted documents should be integrated into one set of treatment guidelines and updated by a standing expert panel as new agents and novel classes of drugs move into the clinic. As with HIV, treatment guidelines could be produced under the aegis of the U.S. Department of Health and Human Services (DHHS).

So far, only the VA, the British HIV Association (BHIVA) and the European Consensus Conference have created coinfection-specific guidelines. These refer primarily to diagnosis and monitoring and HCV in HIV-positive people; little information is provided about treating HIV in people coinfected with HCV. Although HIV treatment guidelines contain some information on HCV treatment, they focus on HIV therapy. Busy clinicians, their patients, and treatment educators would benefit from cross-cutting guidelines.

Deliver Me!

Increasing HCV treatment uptake among mono-and coinfected high-prevalence populations will involve more than new drugs. Hepatitis C is highly common among current and former drug users, a group with a high background prevalence of depression and other psychiatric disorders. Many drug users–both former and current–are considered ineligible for hepatitis C treatment due to concerns about neuropsychiatric side effects of interferon.

Depression, anxiety and mania have been reported in 21-58% of people undergoing HCV treatment (Constant 2005; Raison 2005). A history of depression is associated with a higher risk for developing interferon-associated depression. Anxiety and mood disorders, including depression, are more prevalent among people with chronic hepatitis C than the general population; conversely, HCV is eleven times more prevalent among persons with severe mental illness (Loftis 2006; Rosenberg 2001; Zdilar 2000).

Despite these challenges, hepatitis C can be successfully treated in the context of integrated medical and mental health care, peer education and support programming, and drug treatment services, including methadone and buprenorphine (Litwin 2005; Schaefer 2003; Sylvestre 2005; Taylor 2005).

Efficacy and tolerability of hepatitis C treatment will improve in the coming years. Therapeutic advances

must be accompanied by health care delivery systems suited to the needs of multiply-diagnosed persons. These systems must be created now to meet current needs and in anticipation of future improvements in HCV treatment.

Last Words: If I Told You… I'd Have To Kill You

Unlike the world of HIV research and drug development, the hepatitis C universe is a sparsely populated frontier for treatment activism. The notion of an HCV "community" is often unfamiliar to companies developing HCV therapies. Few companies have met with community members. Some have been reluctant to share even minimal information, such as whether they are investigating a candidate in non-responders, treatment–naïve persons or both. This lack of transparency and communication is
retrograde and unproductive.

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TB Drug and Vaccine Pipeline 2006

by Javid Syed

Tuberculosis (TB), a disease first discovered in 1882, has had a preventive vaccine available since 1921 and has been curable since 1950. Despite these advantages, TB remains the most common–and fatal–curable infectious disease in the world, infecting over two billion people, causing disease in eight million each year and killing two million. The available diagnostic, vaccination, and therapeutic technologies through sputum-smear microscopy, live attenuated bovine TB vaccine Bacillus Calmette-Guérin (BCG), and curative combination chemotherapy, have been insufficient to arrest TB rates, which are rising by 1% a year worldwide and, driven in part by the HIV pandemic, by 4% in sub-Saharan Africa. Nearly all TB-related disease and deaths occur in the developing world (CDC 2005; WHO 2006a; Girard 2005; Young 2006).

TB is caused by the bacterium Mycobacterium tuberculosis (MTB). TB disease is most often a disease of the lungs and the bacterium can be spread from person to person through the air. Symptoms of pulmonary TB usually involve weight loss, fever, night sweats and unexplained cough lasting longer than three weeks. Ninety-percent of the two billion infected with TB have latent tuberculosis infections. Their immune systems have controlled the bacteria; most will never develop active TB. About 5-10% of people with latent infection develop active disease in their lifetimes–half within the first few years of infection and half later in life due to either re-infection or re-activation of latent infection. Latent TB can also become active when a person's immune system has been weakened, thus enabling the TB bacterium to multiply. Active TB infection can disseminate nearly anywhere in the body; if present in the lungs, the bacterium can be coughed into the air on small droplets which may be inhaled by others.

HIV infection greatly increases the risk of developing active TB disease. Among HIV-positive people infected with MTB, the chance of developing active TB disease rises sixfold during the year following HIV infection and continues to increase as the CD4 count progressively declines. In the developing world, TB is a leading cause of death among people with HIV (Girard 2005).

Preventing, treating, and curing TB using drugs and the BCG vaccine are the two key public health strategies used to control tuberculosis. Currently, drug therapy must be taken for six months to cure drug-sensitive TB; in well-administered TB programs, up to 95% of cases can be cured. According to the World Health Organization (WHO), treatment success is 82% for diagnosed sputum smear-positive pulmonary TB cases detected and treated in DOTS programs. During the year 2003, 75% of diagnosed cases were cured, according to WHO's 2006 Global TB Control (WHO 2006b). Multidrug-resistant TB (MDR-TB) requires up to two years of treatment, which is far less successful using available drugs. WHO estimates that fewer than 2% of the world's annual 460,000 new cases of MDR-TB are treated according to WHO guidelines (Stop TB Partnership 2006).

Since the 1950s, combination antibiotic therapy that can cure TB has been available. The duration of treatment required to effect a cure now takes six months, far shorter than the original two-year combination curative regimens. Curative TB treatment requires that four medications be taken daily for two months followed by two medications taken daily for four or six months. Among people coinfected with TB and HIV, several antiretroviral drugs commonly used to treat HIV (such as nevirapine and several protease inhibitors) have problematic interactions with the key TB drug rifampin (rifampicin), thus making it more difficult to treat both diseases simultaneously. In HIV-positive and HIV-negative people, progression from latent to active TB can be prevented using a nine-month course of one drug, isoniazid (INH).

The utility of the TB vaccine in controlling TB is less certain. Although BCG is the most widely administered childhood vaccine in the world, and offers protection from the most severe forms of early childhood TB, its protective efficacy weakens as children mature. Studies indicate that BCG provides protection in the range of 73% for meningeal TB; 77% for miliary TB in children, and diminished to non-existent protection against pulmonary TB in adolescents and adults (Dye 2006). In low-TB prevalence set-

tings such as the U.S., BCG vaccination is not routinely recommended. In other parts of the world, the vaccine is still routinely used in all populations despite little evidence for its effectiveness in reducing pulmonary disease in adolescents or adults. BCG also fails to prevent pulmonary or extrapulmonary TB by re-activation or re-infection among adolescents and adults. Moreover, BCG may cause local and disseminated BCG disease (BCG-itis or BCG-osis), the latter of which may be especially severe–even life-threatening–among children with immune deficiencies, HIV included. (Hesseling 2006).

Clearly, we need better TB drugs that can shorten the time to cure and which can be more easily co-administered with ARVs, as well as safer TB vaccines that not only protect young children from disseminated and meningeal TB but also protect adolescents and adults from reactivated, pulmonary, and extrapulmonary TB disease. New drugs and vaccines will both be required if progress towards the goal of eliminating TB as a public health threat by 2050 is to be realized (Girard 2005; Young 2006).

New TB Drug Product Profile

New TB drugs must address the challenges of current TB therapy. Thus, they need to:

- Decrease the duration and pill burden of treatment
- Have manageable interactions with nevirapine and protease inhibitors
- Treat multidrug-resistant (MDR) TB
- Treat pediatric TB disease

Decreasing the duration and pill burden of treatment

Currently four drugs-rifampin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E) are recommended as first line TB therapy. All four drugs are taken daily for two months during the acute phase of treatment, which is followed by the continuation phase with either four months of rifampin/isoniazid (RH) or six months of ethambutol/isoniazid (EH). The pill burden for this regimen is up to eleven pills a day. Shortening treatment duration and reducing pill burden could improve adherence, increase treatment completion rates, and possibly reduce the risk of developing multidrug-resistant (MDR) TB.

Have manageable interactions with HIV medications

Rifampin (rifampicin) interacts with certain ARVs, particularly nevirapine (an anchor drug in many triple combination regimens used in resource-poor settings) and several ritonavir-boosted protease inhibitors recommended by WHO as standard second-line ARV therapy. Rifampin potently induces the cytochrome P450 isoenzyme CYP3A4, increasing the rate of ARV metabolism, lowering ARV concentrations and diminishing their anti-HIV activity. This type of drug-drug interaction may promote resistance, or, if doses are not adjusted, contribute to excess toxicity.

Treat multidrug-resistant (MDR) TB

Multi-drug resistant TB is defined as TB strains resistant to both rifampin (R) and isoniazid (H). At least 450,000 new MDR-TB cases occur each year, and mortality amongst MDR cases is nearly 50%. Fewer than 2% of the world's cases of MDR-TB are treated according to World Health Organization (WHO) recommended standards for MDR-TB treatment. Second-line TB drugs used to treat MDR-TB are more toxic, 100 times more expensive than first-line therapy and must be taken for nearly two years. New classes of TB drugs that lack cross-resistance to drugs used in first-line therapy are urgently needed to shorten the duration of treatment for MDR-TB and to increase the cure rate to 95% (Stop TB Partnership 2006).

Treat Pediatric TB Disease

Ten percent of TB disease occurs among infants and children, yet TB treatments are rarely studied systematically in children. More systematic investigations of appropriate dosing strategies need to be incorporated into clinical development programs for new TB drugs to assure that emerging drugs can be used in children with TB disease, including those coinfected with HIV who take antiretroviral drugs.

New TB Drugs in Clinical Trials – 2006

Six new drugs are being studied in clinical trials for TB treatment. Two are fluoroquinolones (gatifloxacin and moxifloxacin) already approved and sold worldwide as broad-spectrum antibiotics. The main promise of these fluoroquinolones lies in their potential to shorten curative TB therapy to four months, though definitive evidence from humans is not yet available. The other four drugs are from new classes of anti-TB agents; these drugs have promise for use in first-line TB combination therapy and for MDR-TB. However, these newer agents–from the Global Alliance for TB Drug Development (TB Alliance), Johnson & Johnson/Tibotec, Lupin Pharmaceuticals (India), and Otsuka Pharmaceuticals (Japan)–are all still in early phase I/II testing. Whether any of them will make it through the clinical development pipeline is not yet clear. Meanwhile, safety concerns have emerged concerning gatifloxacin that may ultimately limit its further study and use as TB treatment. Trials are continuing for the time being. The bar may be set relatively high for a new TB drug, since standard four-drug therapy can cure 95% of TB cases. Because millions of people are treated for TB each year, a new drug must match or exceed the efficacy of current treatments while also being safe enough for worldwide use. Activists, research sponsors, public health officials, and TB control programmers have only begun to grapple with the difficult issues facing the field of new TB drug development over the next few years, when-hopefully-several new treatments enter large-scale efficacy trials, in addition to possible treatment-shortening studies with the fluoroquinolones.

TB Drugs in Clinical Trials - July 2006			
Drug Name	**Class**	**Sponsors(s)**	**Phase/Comments**
Gatifloxacin (G) [formerly sold as Tequin® by BMS]	Fluoroquinolone	IDR/OFLOTUB/TDR/Lupin	phase III Sponsors plan to continue phase III studies despite blood sugar problems which led BMS to withdraw Tequin in the U.S. and Europe
Moxifloxacin (M) (Avelox®)	Fluoroquinolone	Bayer, GATDD, JHU, TBTC, UCL	phase II/III Equivalent to E in TBTC 27; TBTC 28; will compare M to H in HRZE
TMC207 (J)	Diarylquinoline	Tibotec/J&J	phase I/II: EBA New mechanism; potential once weekly dosing; active vs. MDR, ARV compatible
PA-824	Nitroimidazopyran	TB Alliance	phase I New class; bactericidal; inhibits lipid membrane synthesis; active in vitro vs. MDR-TB
OPC-67683	Nitroimidazo-oxanzine	Otsuka Pharma	phase I/II: EBA New class
Sudoterb (LL-3858)	Pyrrole	Lupin Pharma	phase I (?) New class; little data

BMS = Bristol-Myers Squibb; TB Alliance = Global Alliance for TB Drug Development; J&J = Johnson & Johnson; JHU = Johns Hopkins University; OFLOTUB Consortium - see 'gatifloxacin' below; TBTC = CDC-funded TB Trials Consortium.

Fluoroquinolones

The fluoroquinolones are a class of broad-spectrum antibiotics that work by binding to proteins (DNA

gyrase and topisomerase IV) involved in bacterial DNA replication. These drugs are licensed and marketed worldwide to treat a broad array of respiratory, gastrointestinal and other infections. Important members of the fluoroquinolone family include ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, ofloxacin, and sparfloxacin. Of these, moxifloxacin and gatifloxacin are most active against TB and have been studied for treating both drug-sensitive and drug-resistant bacilli. Both drugs are approved and widely available. Lack of market incentive discourages companies from studying these widely available drugs as TB therapies. In the fall of 2005, the Global Alliance for TB Drug Development (TB Alliance) signed a collaborative agreement with Bayer to bring moxifloxacin forward. Then, in spring 2006, Bristol-Myers Squibb announced it would discontinue marketing of gatifloxacin due to safety concerns. The European/African OFLOTUB consortium indicates that it plans to continue its ongoing studies of gatifloxacin as a TB agent.

Gatifloxacin (G)

A broad-spectrum fluoroquinolone antibiotic, gatifloxacin (G) was marketed by Bristol-Myers Squibb (BMS) as Tequin in the U.S. and in many other countries until May 2006.

Studies of TB-infected mice showed that 450kg/mg gatifloxacin, plus pyrazinamide (Z) and ethionamide (ETA), five days weekly for twelve weeks, sterilized murine lungs of TB for eight weeks of follow-up. In humans, a phase II clinical trial conducted by the European Commission (EC)–funded OFLOTUB consortium and the South African Medical Research Council (MRC) in Durban investigated the use of G in HIV-positive and HIV-negative individuals with newly diagnosed pulmonary TB. Preliminary results showed that substituting either gatifloxacin (G) or moxifloxacin (M) for ethambutol (E) was more active than HRZE during the first two months of TB treatment (TDR 2005). A phase III trial comparing four months of GRZE/GR versus six months of HRZE/HR is underway. The trial, coordinated by the French Institut de Recherche pour le Recherche pour le Développement (IRD, http://ird.fr) for the OFLOTUB consortium, Lupin Laboratories, and World Health Organization-based Special Programme for Research and Training in Tropical Diseases (TDR), will enroll 2,070 individuals in five African countries and follow them for two years (WHO/TDR 2005). HIV coinfected persons are excluded from the study.

As mentioned above, serious concerns about gatifloxicin toxicity and abnormal blood glucose levels have recently emerged. In February 2006, due to reports of cases of low and high blood sugar in people taking Tequin, BMS was asked to strengthen label warnings for the drug, and FDA issued a public health advisory stating that gatifloxacin should not be used by diabetics or elderly people with kidney disease (FDA 2006). In March 2006, *The New England Journal of Medicine* published a study that examined blood sugar-related abnormalities associated with various fluoroquinolone antibiotics in a population of 1.4 million people aged 66 or older in Ontario, Canada. The report indicated that, when compared to similar individuals who took a macrolide antibiotic or the fluoroquinolones ciprofloxacin or moxifloxacin, persons who took gatifloxacin had a 4.3 fold higher incidence of hypoglycemia-related hospital visits and a 16.7-fold higher incidence of hyperglycemia-related hospital visits (Park-Wyllie 2006). BMS subsequently announced that it would no longer market Tequin. The drug remains widely available from other manufacturers worldwide. Dr. Tom Kanyok, the project director at TDR, has recently confirmed that the phase III gatifloxacin study in Africa continues and that regulatory authorities, ethical review groups, and TB controllers in all five countries where the study is taking place (Benin, Guinea, Kenya, Senegal, and South Africa) are aware of the concerns and believe the study should proceed (Kanyok 2006). Others, however, have questioned the continued use of gatifloxacin in TB research and treatment programs (Yadav 2006). The drug's future is unclear.

Moxifloxacin (M)

Moxifloxacin is considered the most promising anti-TB fluoroquinolone currently in clinical trials. The

drug–marketed by Bayer as Avelox (moxifloxicin hydrochloride) as a broad-spectrum antibiotic in over 100 countries–inhibits MTB through binding to proteins involved in bacterial replication (DNA gyrase and topisomerase IV). Studies in mice suggest that an M-containing regimen may sterilize the lungs more rapidly than conventional regimens. M's sterilizing activity against slow or intermittently reproducing bacteria suggests utility during the continuation phase of TB treatment (Lounis 2001). In mice, M had activity against MDR-TB. Since M is not metabolized by cytochrome P450, it can be used in conjunction with ARVs (Tortoli 2004; Gumbo 2004).

The CDC-funded TB Trials Consortium (TBTC) compared M with E in a phase II trial of standard HRZE vs. HRZM. At four weeks, HRZM had a higher conversion rate to sputum smear negative, though rates of conversion to negative were identical in both arms at two months (Burman 2006). Sixty-three percent of those enrolled in the study were from Africa, where rates of sputum conversion were lower than those seen in North American participants; just 63% of Africans converted to negative at two months compared with 85% of North Americans. HIV status did not affect this observation. Researchers continue to investigate whether other factors such as immune activation, genetic, or geographical co-factors led to this surprising conclusion.

Data from a pharmacokinetic (PK) study examining drug interactions with R showed that the half-life of M was reduced when administered with R and that the area under the curve (AUC, a measure of the availability of the drug in the body) decreased by 27%. The authors also suggested that genetic variations of the human multidrug resistance gene (MDR1) may affect the metabolism of M (Weiner 2006). The TBTC is currently conducting a study comparing the safety and culture conversion rates of HRZE vs. MRZE during the intensive-phase of therapy. The study will enroll 410 participants in North America, Spain, Brazil, Uganda, and South Africa (US National Institutes of Health 2006, Johns Hopkins Medicine 2006).

The biggest news on the M front over the past year came in October 2005 when the TB Alliance and Bayer Health Care announced a phase III trial to study the drug in a treatment- shortening regimen; Bayer has agreed to supply moxifloxacin for the trial. If the method under study is successful, moxifloxacin may be registered for TB indication in a manner that permits affordable access in developing countries. The phase III trial will enlist 1,500; the development program for M will take place in Brazil, Canada, South Africa, Spain, Tanzania, Uganda, the United States, and Zambia and will recruit close to 2,500 people with TB (TB Alliance 2005).

Diarylquinoline

***TMC207 (J)*–**TMC207 is being developed by Tibotec, a subsidiary of Johnson & Johnson. The company has recently entered into partnership with the Global Alliance for TB Drug Development (TB Alliance). Hopefully, this will ensure that, if approved for TB, the drug will be made available to developing countries at an affordable price. The drug belongs to a new class of antibiotics, the diarylquinolines, which specifically inhibit adenosine triphosphate (ATP) synthesis in M. tuberculosis, thus blocking its energy producing mechanism. TMC207 has a long half-life and could potentially be taken once-weekly. Because the drug penetrates and remains in tissue for a significant period of time, it may be effective against latent TB. In mice, when TMC207 replaced isoniazid (H), rifampin (R) or pyrazinamide (Z) in an HRZE regimen, the TMC207-containing treatment combinations performed significantly better. The drug's unique mechanism of inhibition may reduce the potential for cross resistance with other drugs. J also appears to be metabolically compatible with ARVs. No recent published peer-reviewed data are available on clinical trials of TMC207 (Andries 2004). The Global Alliance reports that studies of early bactericidal activity (EBA) in the drug are underway (van Niekerk 2006).

Nitroimidazopyran

PA-824–PA-824, a drug discovered by pathogenesis, which was later acquired by Chiron, is currently being developed by the TB Alliance. The drug's bactericidal activity against M. tuberculosis involves inhibition of cell membrane lipid and protein synthesis. Studies in mice suggest that PA-824 has a level of bactericidal activity during the initial treatment phase comparable to an equipotent dose of isoniazid (H) in humans, though data from clinical studies in humans are needed to confirm this observation. The drug also has sterilization potential comparable to that of isoniazid and rifampin, the two most potent TB first-line drugs currently available. PA-824 is effective against MDR-TB, has potential use against latent TB and has been screened for compatibility with ARVs. Data from human trials for PA-824 are not yet available (Tyagi 2005; Lenaerts 2005; Global Alliance 2004).

Nitroimidazo-oxazole

OPC-67683 (OPC)–Otsuka Pharmaceutical is developing this nitro-dihydroimidazo-oxazole derivative, a mycolic acid biosynthesis inhibitor found to be free of mutagenicity and to possess highly potent activity against TB, including MDR TB. In comparison with R, H, E, streptomycin (S), Z, and PA-824, OPC showed an exceptionally low minimum inhibitory concentration (MIC) range (0.0006 to 0.024 ug/mL) in culture experiments and highly effective therapeutic activity at low doses in animal studies. In a mouse model of TB, OPC did not produce antagonistic effects in combination with other TB drugs, and the combination of OPC with R and Z exhibited the strongest effect, showing at least a 2 month quicker eradication of viable TB bacilli in the lung than seen with the existing standard TB regimen. Other *in vitro* experiments have shown that OPC was not affected by, nor did it affect, the activity of liver microsome enzymes, suggesting that OPC may possibly be used in combination with drugs (including ARVs) that induce or are metabolized by cytochrome P450 enzymes. OPC was also found to be highly active in mice with SCID, which mimics the immune deficiency seen in AIDS patients. OPC is currently in phase II clinical development in TB patients, but no results have been published to date.

Pyrrole

Sudoterb (LL-3858)–Sudoterb (LL-3858) is a pyrrole, a new class of anti-TB agents. The drug, for which few data are pubically available, is sponsored by Lupin Laboratories, who also produces generic gatifloxacin. At ICAAC 2004, the company demonstrated antimicrobial activity in animals. In this study, three months of Sudoterb, along with H, R and Z, was reported to sterilize sensitive and resistant strains of TB. Early clinical trials of this compound are said to be underway (Arora 2004; Smart 2005).

New TB Vaccines

The BCG vaccine is a live attenuated form of Mycobacterium bovis, a mycobacterium that causes TB-like disease in cattle and other animals and can also cause disease in humans. In a paradox of evolutionary history, it appears that M. bovis evolved from MTB sometime after humans domesticated cattle in the past 10,000 years. Developed in 1921 by Albert Calmette and Camille Guérin, this vaccine is given to newborns to prime TB-sensitive immunity so that a protective immune response can be rapidly generated upon exposure to MTB. The BCG vaccine is one of the world's most widely administered vaccines with roughly 100 million doses given to children each year. In high TB prevalence areas, BCG saves many children's lives. In 2002 alone, BCG given to children prevented an estimated 30,000 cases of meningeal TB, a severe form of TB during infancy (Girard 2005; Trunz 2006). The protective effect of BCG diminishes within 10-15 years and usually vanishes by adolescence. Seventy years of research from around the world demonstrates that BCG's protective effects range from over 70% preventive efficacy to zero percent protection among vaccinated adolescents and adults. Re-boosting does

not confer any additional benefit (Young 2006; Xing 2001; Leung 2001). Hypothesized reasons for this variance include:

- Over the past 80 years BCG has slowly evolved away from the original M. bovis strain, losing its immunogenic similarity to MTB in the process. This may be due to selective pressure to reduce the adverse effects of BCG. It is also possible that MTB has undergone evolutionary divergence during this period (Behr 1999; Ridzon 1999).
- BCG immunization protocols vary globally, ranging from one to four immunizations. Little data are available to support boosting, especially at older ages (Xing 2001).
- Prior exposure to environmental mycobacteria might reduce BCG-induced protective immunity to MTB. This is particularly likely in places where other mycobacteria are common, such as in warmer and tropical climates, where reduced BCG efficacy has been seen (Girard 2005).

New TB Vaccine Product Profiles

New strategies are being explored to develop a more effective TB vaccine. Improved understanding of host immunity to TB, the identification of TB genes as well as antigens, the development of improved ways to stimulate immune response through the use of adjuvants (substances that enhance an antigen's ability to stimulate an immune response), and better methods of exposing the antigens to the immune system through vectors have collectively led to new activity in the field. Important findings in the above areas of research include:

- The production of interferon gamma (IFN-$\geq$) by the cellular (Th1) immune system (CD4 and CD8 T cells) is vital for resisting MTB infection. Mice deficient in IFN-$\geq$ are highly susceptible to MTB. Humans with IFN-$\geq$ receptor defects are more susceptible to mycobacterial infections and may develop severe disease after immunization with BCG.
- CD4 cells are stimulated by the early secreted antigens for T cells (ESAT), particularly ESAT-6 and antigen 85 (Ag85), the two most dominant antigens for CD4 T cells.
- Tumor necrosis factor (TNF) and its receptor p55 are also associated with resistance to MTB. Disrupting TNF in the mouse model makes resistant mice more susceptible to TB infection. Humans in whom TNF has been suppressed due to treatment of arthritis or Crohn's disease can experience reactivation of MTB.
- Certain types of CD8 T cells may also inhibit MTB during the latent phase by producing IFN-$\geq$. In non-human primates, gamma-delta T cells with specificity for certain lipids and specific ligands also have a protective function against MTB.
- Interleukin 12 (IL 12) may also play a role in MTB resistance. Mice given IL-12 may eventually develop resistance to MTB.

New tuberculosis vaccine antigen candidates are chosen based on their ability to stimulate IFN-$\geq$ producing (Th1) immune responses directed against MTB-specific antigens. Candidates add an antigen to BCG to make it more potent, combine multiple antigens to be delivered as naked DNA, or deliver them in a harmless vector. These new vaccination approaches will be investigated as primary vaccines and as boosters intended to sustain and expand the protection offered by BCG in early childhood. These new vaccine development strategies are discussed in detail below.

Subunit protein vaccines

Subunit vaccines that are either given alone or with BCG. These are MTB antigens combined with an adjuvant, naked DNA, or recombinant MTB proteins expressing an antigen that produces an immune

response against TB. Most are early secreted antigens produced during an early phase of MTB infection and would be appropriate for pre-exposure vaccination. These antigens include Ag85 and ESAT6. The former is common to MTB and BCG and the later is an antigen specific to MTB. Proteins produced during the latency period are also being investigated for a post-exposure vaccine. Subunit vaccines usually require an adjuvant to stimulate a strong Th1 immune response. Ag85A-ESAT-6 (recombinant antigens) and MVA-85A (recombinant modified virus Ankara carrying MTB antigen) are vaccine candidates currently being studied that have been developed using this strategy.

Attenuated or recombinant live mycobacterial vaccines

MTB mutant vaccines would be attenuated by deleting genes, rendering them less pathogenic. There is limited information on the efficacy of mutant MTB as a vaccine. Concerns about the genetic stability of the mutants also raise cautions about the use of such vaccine candidates in clinical trials. To prevent reversion of the mutant MTB to a pathogenic form, a vaccine candidate should have two independent gene deletions. Mutants of MTB that have virulence-causing genes deleted may also be genetically modified to enhance immunogenicity.

Recombinant BCG vaccine candidates are versions of BCG in which certain genetic features of MTB have been introduced. BCG lacks about 130 genes present in MTB. The introduction of some of these MTB genes may increase its capacity to stimulate an immune response without it becoming pathogenic. Examples of this approach to vaccine development strategy are the rBCG-Ag85 and rBCG::D (Kaufman 2005).

The current TB vaccine pipeline contains candidates being studied in humans which employ many of the above strategies. Depending on the type of antigen or specific immune stimulating strategy involved, the vaccines might be more appropriate for use as pre-exposure, post-exposure, or in conjunc-

TB Vaccine Candidates in Clinical Trials			
Viral vectored naked DNA:			
Vaccine	**Type**	**Sponsors(s)**	**Phase/Comments**
MVA-85A	Vaccinia virus + AG85a Ankara	Oxford	Phase 2, modified Vaccinia strain expressing MTB Antigen Ag85A; will be studied as post-exposure vaccine
Recombinant/modified BCG:			
Vaccine	**Type**	**Sponsors(s)**	**Phase/Comments**
rBCG::D	rBCG + urease-deleted	Max Planck Institute	Phase I, rBCG containing a gene for listeriolysin and lacking gene for urease
rBCG30	rBCG vacccine	Aeras, UCLA	Phase 1; development halted due to FDA/EMEA concerns re: hygromycin anti-biotic gene
Non-BCG subunits:			
Vaccine	**Type**	**Sponsors(s)**	**Phase/Comments**
Ag85B-ESAT6	Recombinant protein	Statens Serum Institute	Phase 1; two MTB antigens, Ag85B-ESAT6
Putative therapeutic immunogen:			
Vaccine	**Type**	**Sponsors(s)**	**Phase/Comments**
SRL172	heat-killed *M. vaccae*	SR Pharma, Dartmouth	Few positive data from multiple clinical trials In drug-sensitive TB; in phase 2 as therapeutic vaccine inMDR-TB.

tion with TB therapy. These candidates are also being studied to see if they can be given in combination with BCG to boost its immunogenicity. Regardless of how the vaccines are administered, they need to be affordable, accessible, and able to mount an immune response more effective and durable than that provided by the BCG vaccine. Ideally, new vaccines should also be delivered in a way that minimizes the number of health care visits. The need for vaccines that can be used at different stages of TB infection and for pre- or post-exposure to TB may mean that more than one vaccine needs to be developed (Kaufman 2005; Reed 2003; Girard 2005; Young 2006). Vaccines in the current pipeline are being studied in animal models; the guinea pig model is commonly used because these animals are susceptible to low doses of MTB, develop strong delayed-hypersensitivity skin reactions to TB, and develop characteristic TB lesions and cavities of dead TB-damaged lung tissue. However, animal models are most useful for investigating pre-exposure immunization; a gap remains in the technology needed for developing vaccines that are effective in preventing disease in people with prior TB exposure (WHO 2006c).

Viral vectored naked DNA

*MVA-85A–*The modified vaccinia Ankara (MVA) is an attenuated strain of Vaccinia (cowpox) virus that was developed towards the end of the smallpox eradication campaign and has been administered to more than 100,000 people without significant side effects. Developed at Oxford University, this vaccine contains MVA modified to expresses a major TB antigen, Ag85A, which stimulates a strong immune response. It is a boosting vaccine designed to increase a preexisting immune response. This strategy employs two different vaccines: BCG, followed by MVA-85A given a few weeks later. Using different vaccines to boost a primary immune response is a heterologous prime-boost strategy (Goonetilleke 2003). In mice infected by TB, MVA-85A boosted vaccination was significantly more protective than BCG alone. In humans, MVA-85A boosting produced equivalent immune responses regardless of whether BCG had been given a few weeks or 10 years before, suggesting that a MVA-85A boost in adolescence may be protective (Williams 2005). BCG-naive, healthy volunteers given MVA-85A in phase 1 trials produced high levels of antigen-specific IFN-secreting T cells. Trial participants previously vaccinated with BCG produced thirty-fold more IFN-secreting T-cells at 24 weeks after vaccination (McShane 2004). BCG is hypothesized to lose its protective ability due to immune responses triggered by environmental mycobacteria. The MVA-85A can potentially capitalize on this pre-existing immune response by boosting it and enhancing the protection against TB. MVA-85A could be used as a post-exposure vaccine. Furthermore, since it's non-replicating, MVA vaccine is also considered to be safe for use in people with HIV (Williams & Goonetilleke, 2005).

Recombinant/modified BCG

*rBCG::D ureC-llo–*This is a form of BCG containing a gene for listeriolysin (Hly) and lacking the gene for urease. It is hypothesized that BCG may be unable to stimulate an immune response and prevent TB disease, because it is identified as a foreign body and removed via phagocytosis. However, BCG deficient in urease and enhanced with Hly is able to perforate the phagosome and present itself to the immune system (Grode 2005; Girard 2005; Max Planck Society 2005). After infection with aerosolized M. tuberculosis, mice vaccinated with BCG were compared to unvaccinated mice and mice vaccinated with rBCG::D ureC-llo. Mice vaccinated with the latter had less TB in their lungs after 150 days. However, there was no significant difference between BCG and rBCG::D ure C-llo-vaccinated mice at 30 or 90 days post-infection. When compared to the naive mice, rBCG::D ureC-llo produced a 1,000-fold reduction of MTB in the lungs. The rBCG::D ureC-llo vaccine protected mice from infection with the Beijing MDR-TB strain, whereas the parental BCG showed no protection at all. Information about clinical trials due to start in 2006 is not yet available (Grode 2005; Doherty 2006).

*rBCG30–*This modified BCG vaccine has a gene inserted into a parental BCG strain that over-expresses a 30-kDa MTB protein found in MTB-infected human macrophages as well as in broth culture. This

approach was supported by earlier animal experiments in which guinea pigs immunized with rBCG30 then exposed to aerosolized TB had fewer TB bacteria in their lungs, liver, and spleens than animals immunized with BCG alone. Though the vaccine was well tolerated in healthy volunteers, rBCG30 contains an antibiotic marker gene for Hygromycin, which can kill bacteria and fungi by inhibiting protein synthesis. Therefore, the FDA and the European Medicines Evaluation Agency (EMEA) have requested that further study of this particular recombinant form be halted (Horwitz 2006, Sadoff 2004).

Subunit proteins

Ag85B-ESAT6–Ag85B-ESAT6 is a recombinant vaccine containing the MTB proteins Ag85B and ESAT6. The ESAT6 antigen is also being studied as a potential new diagnostic for TB since it was seen that newly PPD-positive people and people with active TB produced more ESAT6 reactive IFN-gamma cells than those who were BCG vaccinated or healthy. Both Ag85B and ESAT6 produce significant immune responses during early stages of TB infection. Mice studies have shown that the combined recombinant forms of these proteins are more potent in terms of the degree of protection they induced (measured by IFN-$\geq$ release) than Ag85B and ESAT6 given separately as single antigens. No antigenic competition was seen in mice, and immune responses to one protein did not prevent the development of an immune response to the other. Compared with naïve mice, and mice receiving separate antigens, mice vaccinated with the dual protein/adjuvant combination had significantly less colony forming units of MTB in their lungs and spleens upon MTB challenge ten weeks post-immunization. Compared with BCG, the Th1 immunological memory produced by the recombinant vaccine at 10 weeks was comparable. However, the levels of protection in the lung for BCG waned by 30 weeks when compared with the levels of protection produced by Ag85B-ESAT6. In one mice experiment, it was seen that, when the control was BCG vaccinated mice, the recombinant antigens produced a level of protection less than BCG and less than each of the proteins alone. Furthermore, it is hypothesized that BCG protection varies greatly around the world due to the differences in BCG and MTB. Therefore, having a recombinant fusion of two MTB proteins may stimulate an immune response that will have greater protective capacity. Based on the above data, the vaccine is now in phase I trials. No other information is yet available (Olsen 2000; Kamath 1999; Doherty 2006; Ulrichs 2000).

Mtb72f–Mtb72f is a vaccine composed of two MTB antigens (Rv1196 nad Rv1025) developed at Corixa Corporation and acquired by GlaxoSmithKline in 2005. Data presented by Mark Alderson of Corixa Corporation showed that the mean survival time (MST) of MTb72f vaccinated guinea pigs was 57 weeks, compared to 47.5 weeks among BCG vaccinated mice and 18.5 weeks for controls. This effect was stronger when MTb72f was used to boost BCG; MTb72f-boosted BCG increased the MST to 66 weeks in guinea pigs while MST with BCG alone was 41 weeks, and 19 weeks in controls (Alderson 2006). A study comparing the MTb72F vaccine delivered as naked DNA to formulations of MTb72f with adjuvants AS01B and AS02A found that the formulation with MTb72f in adjuvant AS02A, although it elicited a weaker immune response, was more stable, making it the preferred formulation of the MTb72f vaccine. Guinea pigs vaccinated by either DNA or AS02A adjuvant form of MTb72f showed a survival comparable to BCG greater than one year after being exposed to infectious TB. However results from another study conducted by GSK and Aeras found that guinea pigs vaccinated with BCG boosted with MTb72f did not have an increased rate of survival (Skeiky 2004; Aeras 2006). In addition to this animal data, MTb72f in adjuvant AS02A was tested in twelve PPD-negative adults who did not have latent or active TB. This study showed that all three doses of the vaccine induced antibody and T-cell responses. No serious adverse effects were reported. Another phase I study in 50 PPD-negative healthy subjects administered two antigen dose levels (10 and 40 mg) intramuscularly at 0, 1, 2 months followed by a booster at nine months. This study showed that both doses induced significant antibody response compared to antigen or adjuvant alone. There were no safety concerns from this study either. However, preliminary data from a third study in 40 PPD-positive subjects aged 18-45 showed that volunteers recently infected with TB had injection site reactions or reactions at distal site reactions. In another study with non-recently infected subjects, the safety profile was acceptable.

Results from the study that showed safety concerns are being reviewed. Another variant of MTb72f (M72) has been designed that is stable in AS01B (Aeras 2006).

Putative Theraputic Immunogen:

SRL 172–SRL 172 is a heat-killed Mycobacterium vaccae (M. vaccae) that is not known to cause disease in humans or animals. Heat-killed M. vaccae is administered with the intent of inducing a Th1 immune response leading to the production of cytokines such as IFN-gamma, interleukin 12, and TNF-alpha. One immune response study in TB patients showed that SRL172 suppresses pre-existing Th2 immune responses that produce interleukin 4, a cytokine which can downregulate the desired Th1 response, making it less effective against MTB (SR Pharma; Doherty 2006).

SRL 172 is being studied for MDR TB as well as for its therapeutic effects during treatment. However results are varied. A double-blinded study of HIV-positive patients with pulmonary TB looked at whether a single injection of SRL172 within two weeks of starting an eight-month TB treatment regimen would impact mortality. In that study, 386 of 1229 HIV-positive pulmonary TB patients received SRL172 along with their TB treatment. Though there were no adverse effects, the vaccine didn't have any significant impact of bacteriological or mortality outcome. A comment in *The Journal of Respiratory Medicine* discussed the immunotherapy value of heat killed Mycobacterium vaccae in treating multidrug-resistant TB based on the following data. This data on 337 patients collected from TB centers in various parts of the world were grouped according to MDR-TB duration of greater or less than two years. The number of transdermal M. vaccae injections varied from one to twelve doses, treatment regimens varied greatly, and there was no control arm. The authors maintained that among MDR patients expected to die, the addition of up to two doses of M. vaccae allegedly helped cure 18 of 22 patients who had the disease for less than two years. Multiple M. vaccae doses were also said to help cure patients who had MDR-TB for longer periods of time and thus few therapeutic options. The authors suggest that these preliminary data may justify conducting a randomized clinical trial in MDR-TB patients to determine whether these observations were accurate and scientifically valid (Stanford 2001). In a small study, SRL172 was given along with short-course TB treatment to twelve patients, compared with ten who received TB treatment alone. These persons were HIV- negative and newly diagnosed pulmonary TB patients. SRL172 injections were given on the 1st, 30th, and 60th day of chemotherapy. All patients were given sputum tests, chest X-rays and blood tests. In this small study, persons given SRL172 were said to have experienced a faster and more complete clinical improvement, with earlier culture conversion and better resolution of disease as measured by chest X-ray (CXR). Currently a five year, 2274 HIV-positive patient study called DarDar is being conducted in Dares Salam, Tanzania by Dartmouth Medical School to look at the impact of SRL172 on disseminated TB in HIV-positive people (Dlugvitsky 2006).

The results of poorly designed, sometimes retrospective and not always well-controlled SRL172 studies were demonstrated in an external Cochrane review of seven trials of M. vaccae to treat tuberculosis. Overall, this analysis showed no difference in mortality between trial participants who received M. vaccae and those who did not. The review also found that receiving immunotherapy did not have a consistent impact on sputum culture conversion and was associated with a greater degree of local adverse effects (de Bruyn 2003).

Policy Recommendations

The Global Plan To Stop TB 2006-2015 lays out a roadmap to achieve the Stop TB Partnership's definition of the TB-related Millennium Development Goals (MDGs) to reduce TB incidence and death globally by 50% compared with the baseline year of 1990 (Stop TB Partnership 2006). TB was not actually named in the UN Millennium Summit Declaration, being referred to among "other infectious diseases" after HIV and malaria. The Global Plan will not achieve the TB related goals in Africa and Eastern

Europe due to HIV-related TB and MDR-TB, respectively (Ibid).

Ultimately, the Partnership seeks to eliminate TB as a public health threat by 2050 but acknowledges that this will not be possible without greater resources and new diagnostics, drugs, and vaccines that are cheaper, safer, and more effective.

The fact that a third of the world's population is already infected with TB indicates that a vaccination strategy cannot be focused solely on neonates or by using BCG alone but also requires post-exposure strategies as well as therapeutic vaccinations that can be given alongside TB treatment to reduce treatment duration.

Furthermore, current TB treatments have substantial drawbacks in terms of length of treatment, drug interactions with HIV medications, and adverse effects.

These challenges in the field of TB treatment and vaccines are being addressed more aggressively than before. Since TB is a disease of the poor, market incentives are weak for private sector investment in research and development of new TB drugs. Furthermore, because TB is considered treatable and BCG considered effective, the public sector has neglected TB. The current lack of public sector support is evidenced by levels and sources of funding for TB drugs, vaccines, and diagnostics research and development in 2004 and 2005. The major support for these initiatives came from U.S. National Institutes of Health, the Bill & Melinda Gates Foundation, the U.K. Medical Research Council, the U.S. Centers for Disease Control & Prevention, and the European Commission's 6th Framework.

Despite the emergence of four new classes of anti-TB drugs and the possibility for shortening treatment offered by moxifloxacin, global infrastructure to support clinical trials of new drugs and vaccines for TB is only beginning to be developed. The top twenty funders of TB research globally spend less than $400 million on the disease each year, while just one funder, the NIH, spends almost $2.9 billion on HIV/AIDS research. Clearly research progress against HIV/AIDS in the past twenty years–particularly in terms of treatment research–has benefited from focused community advocacy, which created political will and helped mobilize scientific resources, attracted public and private sector investment, and resulted in a healthy drug development pipeline.

By comparison, low annual funding for TB research is a measure of insufficient political will to leverage support for TB control in relation to its deadly global impact. The product development partnership (PDP) or public private partnerships (PPP) such as the Aeras Global TB Vaccine Foundation and the TB Alliance are beginning to play a catalytic role in bringing together public and private institutions to capitalize on basic science and other expertise of the public sector and provide incentives to the private sector by sharing investment risks, thereby rejuvenating the pipeline for TB treatment and vaccine R & D. The PPPs' product development approach is undertaken with commitment to ensure that the new products are accessible for people bearing the greatest disease burden. However, these non-profit PPPs cannot and should not shoulder the full responsibility for developing tools to address this public health need. The public sector, both in donor and high burden countries, must assume a leading role in TB research and program activities.

The under-funding of TB must be addressed to fill the gaps identified by The Global Plan To Stop TB 2006-2015. The Global Plan predicts that $56 billion will be needed over the next ten years, a threefold increase over current funding levels. $31 of the needed $56 billion is not yet available. The Global Plan estimates a research funding need of $9 billion and a research funding gap of $6 billion over the next decade (Stop TB Partnership 2006). However, we believe that the funding gap is greater–both because fewer funds are available for TB new tools research in 2006 than The Global Plan projected, and because the funding needs are likely to be greater than those estimated in The Global Plan (Feuer 2006).

In order to fund this gap, a political movement is needed to underscore the fact that TB is a political issue. The TB political movement needs a coordinated effort which could develop partnership between civil society organizations, public leaders, researchers and funders. In order for this type of collaboration to be successful, the following issues must be addressed:

- Community advocacy networks, especially those working with communities at greatest risk for TB, must engage their constituencies and allies to ensure that TB is included in the advocacy agenda. This requires that people infected or at risk for TB disease become vital partners in all aspects of TB research and program planning, implementation, and evaluation. Informed and empowered networks of people at risk for, or living with, TB (including networks of HIV-positive people) can play a significant role in advocating for political support, and strengthening TB program and research efforts.
- Increase transparency and tracking of TB funding to allow the generation of accurate estimates and the development of well-informed advocacy platforms.
- Persuade political, public health, and scientific leaders to intensify public sector investment in TB research. Private foundations and public private partnerships cannot succeed without strong public sector support. Together, these collaborations provide resources for TB research as well as for programs to ensure that health is a right that every person can enjoy. This includes the funding of basic and operational research which will ensure that a robust pipeline exists, and that any TB drugs and vaccines approved are accessible to people in greatest need.

Such strategies can support the goals for TB control and elimination in ways that also address interlocking socioeconomic and political inequalities at the core of TB as a health issue. Increased collaboration between these constituencies can strike at the heart of the issues (including poverty, stigma, and marginalization) that prevent those who are most likely to get sick and die of TB–people who have the most to gain from the control of TB - from participating in the struggle to eliminate the disease.

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