

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

by Rob Camp, Richard Jefferys, Tracy Swan & Javid Syed edited by Mark Harrington & Bob Huff

> Treatment Action Group New York, NY, USA

> > July 2005

e thymidine • BI-201 • Racivir (PSI 5004) • TMC-278 • Diarylpyrimidine (DAPY) • 640385 • Reverset (D-D4FC) • JTK-303 • UK-427 (maraviroc) • Amdoxovir • AMD-070 • Vicriviro LIPO-5 • GTU-Multi-HIV • pHIS-HIV-B • rFPV-HIV-B • ADMVA • GSK Protein HIV Vaccine FBC-M335 (MVA) • TBC-F357 (FPV) • TBC-F349 (FPV) • LIPO-4T (LPHIV-1) • LFn-p24 • F G • Oligomeric gp140/MF59 • VRC-HIVDNA-009-00-VP • PolyEnv1 • ISS P-001 • EP HIV-• BufferGel • Lactin-V • Protected Lactobacilli in combination with BZK • Tenofovir/PMPA G Jose acetate/CAP) • Lime Juice • TMC120 • UC-781 • VivaGel (SPL7013 gel) • ALVAC Ad5 • Autologous dendritic cells pulsed w/ALVAC • Autologous dendritic cell HIV vaccinatio x • Tat vaccine • GTU-nef DNA vaccine • Interleukin-2 (IL-2) • HE2000 • Pegasys (peginte L-4/IL-13 trap • Serostim • Tucaresol • MDX-010 anti-CTLA4 antibody • Cyclosporine A • 96 • HGTV43 • M870 • Vertex • VX-950 • Idenix • Valopicitabine (NM283) • JTK-003 mplant • Albuferon • Celgosivir (MBI-3253) • IC41 • INN0101 • Tarvicin • ANA971 (oral) floxacin, Tequin • J, TMC207 (ex R207910) • LL-3858 • M, moxifloxacin, Avelox • PA-824 Acknowledgements. Thanks to our intrepid editors, Bob Huff, copy-editor Andrea Dailey, and proof-reader Jen Curry, to awesome layout expert Lei Chou, to webmaster Joel Beard, to Joe McConnell for handling administrative matters related to the report, and most of all to the board and supporters of TAG for making our work possible.

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.

For more information:

Treatment Action Group 611 Broadway, Suite 608 New York, NY 10012 1.212.253.7922 – tel. 1.212.253.7923 – fax www.treatmentactiongroup.org

This report is dedicated to

Charles Clifton (1959-2004) & Keith Cylar (1958-2004)

Table of contents

- i What's in the Pipeline? by Mark Harrington
- 1 Antiretrovirals by Rob Camp
- **17 Immune-Based Therapies and Preventive Technologies** by Richard Jefferys
- **39 Hepatitis C Virus (HCV) Treatment** by Tracy Swan
- **49 Tuberculosis (TB) Treatment** by Javid Syed

What's in the Pipeline?

by Mark Harrington

This overview of the antiretroviral, vaccine, microbicide, immune-based therapy, and anti-HCV and TB drug pipeline (focusing on products that have advanced to clinical testing in humans) reveals the state of research on AIDS and its most common global co-infections in mid-2005. The news is mixed.

The antiretroviral (ARV) pipeline is surprisingly robust. Despite the availability of over 20 FDA approved anti-HIV drugs, a variety of companies both large and small continue to invest in a broad array of potential new competitors. At least seven drugs are in early phase I studies, six in phase I/II, and eleven in randomized phase II/III efficacy studies. Rob Camp's ARV pipeline shows five nucleoside analogues, many of which are designed to treat virus resistant to 3TC or FTC. There are six non-nucleoside reverse transcriptase inhibitors (NNRTIs), including two from Tibotec, as well as the now moribund capravirine, an Agouron legacy at Pfizer. Two protease inhibitors are being studied, including Tibotec's TMC-114/r, which is making a fast track for FDA accelerated approval filing in early 2006. It's too soon to tell whether any of these drugs in existing, wellpopulated drug classes will be able to displace any of their well-established forebears. More exciting is the activity in the entry inhibitors family, including gp120 blockers from BMS, three hotly competitive CCR5 inhibitors from GSK, Pfizer and Schering, a slow-moving CXCR4 inhibitor from Anormed, and the high-tech, likely to be expensive even if effective PRO-542 CD4-IgG fusion protein, as well as TNX-355, an anti-CD4 monoclonal antibody from Tanox. Panacos has PA-457, a budding inhibitor, and Merck and Gilead have integrase inhibitors entering the clinic. Finally, BioInvent has a Tat protein inhibitor, and the morning after pill RU-486 (mifepristone) is being studied by the Adult AIDS Clinical Trials Group (AACTG) as a potential antiretroviral (it inhibits the interaction between HIV's Vpr protein and cellular glucocorticoid receptors).

The new classes of drugs present hazards. No one knows whether the CCR5 blockers will accelerate a potentially catastrophic HIV phenotype switch to faster-replicating X4 strains. The only assay used to determine prevalence of R5 or X4 HIV strains, ViroLogics' PhenoSense, is expensive, time-consuming and the company currently lacks the capacity to scale up the test if it becomes commercially necessary; moreover it could add \$1,000 to the cost of the standard of care.

The current race to develop the CCR5 inhibitors, and the entry of other classes into clinical trials, demonstrates the scientific payoff from two decades of significant public and private investment in HIV research. This progress is now threatened by the flattening budget at NIH, which is scheduled to rise by just 2% next year. Industry consolidation and the departure of some companies from infectious disease research may also threaten future developments in this area.

Things are more sobering on the HIV vaccine front. As Richard Jefferys' overview demonstrates, while there are 17 vaccine candidates in phase I, many utilize similar approaches. Just four vaccine candidates are in phase I/II. Hopes are moderate for the Merck adenovirus vector vaccine now in Phase IIb, which may be an improvement on previous vaccines in its ability to stimulate anti-HIV cell-mediated immunity (CMI), and are vanishingly low for the NIH/Department of Defense's scientifically indefensible but logistically unstoppable ALVAC vCP1521 canarypox vector/AIDSVAX prime-boost vaccine trial now underway in Thailand at a cost of over \$150 million. On the therapeutic side, at least 13 therapeutic vaccines are also relevant here. The HIV vaccine field awaits a breakthrough in basic science, one which would be particularly available if it led to the

development of a vaccine which conferred effective neutralizing antibodies against common HIV strains found in humans.

The HIV microbicide field, in contrast, is surprisingly robust, and has recently caught up with and overcome vaccines. At least four candidate microbicides are in phase III, five are in phase II, and six are in phase I. Their mechanisms of activity are heterogeneous, ranging from soaps to acid-buffering agents to seaweed derivatives to anti-HIV compounds. Perhaps the lack of validated animal models has actually sped entry of potential microbicides into human efficacy trials. The downside of several concurrent failed studies could be dangerous, but the need for new and effective prevention approaches validates the rapid movement in this field.

More controversial, yet supported by strong evidence from animal studies, is the use of tenofovir DF (Viread®) as pre-exposure prophylaxis (PrEP) to prevent sexual – and possibly parenteral – transmission of HIV. Small-to-medium sized phase II trials are underway in Atlanta and San Francisco, with larger phase II/III studies underway or planned in Botswana, Ghana, and possibly Thailand. These studies have been dogged by controversy, with the main issues being the adequacy or lack thereof of the pre-trial community consultation and informed consent, linkages to HIV treatment programs for those found to be infected at baseline or in the course of the study, and – in the case of Thailand – the lack of access to needle exchange in a study designed to examine HIV transmission among injecting drug users. PrEP studies have already been canceled in Cambodia and suspended in Cameroon. Hopefully a recent series of consultations in two African sites, Geneva, Seattle, and Thailand among research sponsors, community activists, and others will help resolve the outstanding issues to move this promising research forward.

Richard Jefferys also gives an overview of the twelve cytokines and gene therapy approaches which are in clinical trials, including the perennial interleukin-2 (IL-2), now in a large phase III trial in many countries, and five cellular and gene therapy approaches. More progress in this area depends on new insights into HIV pathogenesis and human immunology.

The hepatitis C virus (HCV) infects over 129 million people worldwide and has infected over 3.8 million people in the United States. HCV can lead to cirrhosis and liver cancer, and progresses more rapidly in HIV-positive people. End-stage liver disease from HCV has become one of the leading causes of death among people with HIV in the USA and parts of Europe. Current treatment for HCV relies on a combination of pegylated interferon and ribavirin. It appears to eradicate the virus in approximately 50% of those without HIV infection, but is far less effective for those with HIV, with HCV genotype 1, or African-Americans. Efficacy of current hepatitis C treatment is limited by a range of side effects and toxicities. The good news is that at least 17 candidate anti-HCV drugs are in clinical trials, most of them small molecules with new mechanisms of activity, but some new types and formulations of alpha interferon as well.

After forty years with no new major drugs, there are now six new candidate therapies in the clinical pipeline to treat tuberculosis (TB), an age-old killer which infects up to two billion people worldwide, causes disease in nine million, and kills two million each year. Javid Syed's review of the TB drug pipeline shows that recent investment in TB research is beginning to pay off, with two fluoroquinolones (gati- and moxifloxacin) along with at least three novel drug classes. The new TB drugs offer the potential to shorten the six-month TB treatment regimen, to simplify co-administration

of TB treatment with ART, and also to treat multi-drug resistant (MDR) TB. Since TB is the most common AIDS-related co-infection worldwide, and MDR-TB is rampant in former Soviet states and elsewhere in Asia, such new candidates are overdue.

I have already mentioned the danger current US funding cuts and industry trends pose to AIDS research. There are additional threats to the HIV, HCV, and TB pipelines. The National Institutes of Health (NIH) will spend over \$2.7 billion this year on AIDS research. However, it spends little over \$100 million on TB, and even less on HCV research. There is virtually no funding for clinical trials for TB and HCV drugs. Substantially increased public investment is needed not only in basic research on the interactions of HIV, TB, and HCV with the immune system, but on clinical trials infrastructure in the places and settings where these three epidemics are rampant. Co-infected people are often excluded from clinical trials.

Research is only part of what is needed to make life better for people living with HIV, TB, and/or HCV. These diseases target vulnerable people who often suffer from social exclusion and political discrimination. Current policies on drug use and sexual diversity are driving up infection rates. The current crisis caused by inadequate FDA oversight of approved drugs post-marketing also poses dangers to people who may benefit, but may also be harmed by new drugs. Stronger post-marketing surveillance systems, stronger FDA authority to mandate post-marketing studies when necessary, and curbs on irresponsible and uninformative direct-to-consumer advertising campaigns are also needed to ensure that new drugs, once they reach the market, continue to be studied to determine their effects in real-world populations.

We are encouraged that industry continues to invest in new drugs for HIV, TB, and HCV. But substantially increased public investment in basic and clinical science, free and universal access to effective prevention and treatment interventions, and a strong but flexible regulatory environment are all critical to assuring a healthy drug development pipeline and healthy use of the drugs after approval. And ultimately, none of this will be secured without informed communities who have access to the prevention, treatment, and information they need to live.

Antiretroviral Pipeline 2005

by Rob Camp

In Memory of Arjen Broekhuizen

Introduction

The antiretroviral (ARV) pipeline is important because current treatments are imperfect. In the most recent U.S. guidelines on antiretroviral treatment, there are eleven pages of tables of adverse effects and how to manage them. Some are potentially life-threatening, others chronic, cumulative, overlapping, and sometimes irreversible (DHHS 2005).

Although some current drugs are relatively benign, few combination regimens are wholly non-toxic, though some may be less so than others.

The efficacy and durability of initial highly active antiretroviral therapy (HAART) combination therapy regimens appears to have increased in the years since HAART was introduced in 1996. In the Johns Hopkins HIV Cohort, six-month viral suppression to below 400 HIV-RNA copies/mL increased from 43.8% in 1996 to 72.4% in 2001-2002; the comparable levels at twelve months were 60.1% and 79.9%, respectively (Moore 2005). Combination antiretroviral therapy (ART) doesn't cure, but the progressive introduction of new drugs and classes, simplified treatment regimens, and (in some cases) reduced toxicity and adherence burdens have led to sustained improvements in HIV-related morbidity and mortality in the U.S. and other developed countries.

Nonetheless, because of significant long-term toxicity and the growing numbers of people experiencing antiretroviral treatment failure, new drugs and drug classes continue to be urgently needed. Given stable domestic rates of HIV infection (~40,000 new infections in the U.S. per year), rising rates worldwide (~5 million new infections per year), and extended survival with HIV with broadening access to ART, this need will only grow in coming years.

Twenty-four new anti-HIV drugs are now in clinical trials. None of these will be a cure for AIDS. Strategically, we may be moving toward fewer pills a day, but eradication of HIV with current therapeutic approaches does not look feasible.

I. Landscape of Current Treatment

Over the past few years, the community has been repeating, to pharmaceutical companies, to FDA, and to the medical community, the information gaps characteristic of new ARVs at the time of approval and—all too often—persisting long afterwards (Camp 2004):

- More data should be available on pharmacokinetics of drugs in diverse populations, including women; African-Americans and other ethnic groups; people with hepatic or renal impairment; people with HBV, HCV or TB infections; and children.
- More drug-drug interaction studies should be completed at the time of approval, including studies with methadone, birth control hormones, TB drugs such as rifampin, and of course with the most commonly used antiretroviral drugs, those on the market and those still under study.
- Study populations need to reflect the makeup of the epidemic by adequately representing women and people of color. New relationships need to be developed with clinics capable of enrolling more diverse groups of individuals.

- After drugs have been approved, promises made by companies to continue postmarketing research should not be allowed to languish. Currently the agency has no effective way to compel completion of these Phase IV "good-faith" commitments, and Congress should pass legislation to give the FDA more authority in this area.
- Better systems are urgently needed to monitor chronic and long-term side effects after drugs are approved. The current adverse events reporting system is voluntary and may miss substantial toxicity. A network of "sentinel practices" to report unusual symptoms might be a viable enhancement to the current inadequate MedWatch 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 major concern for the community

These "themes", in one way or another, reflect the questions that we come home with after approval of every drug, and to which we don't ever seem to get answers: What are the drug's benefits? What are its risks? How should the drug be used and managed? Who will benefit? What is still unknown?

After the recent approval hearing for tipranavir/ritonavir (TPV/R), there are more unknowns than ever before, or more agreement on accepting the unknowns than ever before. At the tipranavir hearing on 19 May 2005, the Chair of the FDA's Antiviral Drugs Advisory Committee, Dr. Janet Englund, stated, "At every meeting we have, the same issues come up again and again, like the lack of adequate numbers of women. We, the medical community, aren't comfortable with how to use the drug in women." The final vote was 11 in favor "with reservations", 3 en contra (http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4139b1.htm).

Also, studies of future therapies need to keep in mind those pharmacokinetic (PK) issues that are constantly relegated to "we will look at that later". What is the role of pharmacokinetic data in the evaluation of dosing regimens? Are the present correlations of exposure measures enough to advise toxicity (Cmin, AUC, etc)? Which exposure measures should be considered when providing labeling information on concomitant administration of antiretrovirals? Once an alternate regimen has been identified in adults, should we expect identical PK profiles in children (ie, children and neonates as small adults)? What kinds of studies are needed to better define pharmacokinetic/ pharmacodynamic relationships for antiretroviral drugs?

II. Desired Elements of Future Therapies

Future therapies need to be affordable, offer a minimum of side effects, have no cross-resistance, and be simple to adhere to; it goes without saying that they also need to be effective, which most first-line drugs already are. In advanced and salvage settings, however, the bar for approval is much lower. FDA is now approving drugs that are 35% effective at 24 weeks in highly pretreated individuals because the drugs appear to offer some benefit. The risk that accompanies that benefit needs to be more clearly defined in the populations that will be using the drug in the real world.



Figure. Replication Cycle of HIV and Drug Targets

III. Pipeline Review

Although many drugs are in the clinical pipeline, a closer look at the chart on the following page reveals that most are far from approval. There are just a handful of drugs in phases IIb/III. Of these, four are nucleoside reverse transcriptase inhibitors (NRTIs) unlikely to offer a major step forward, while two are NNRTIs—none of which appears to be advancing quickly—while five to six are members of new classes of entry inhibitors, including the controversial CCR5 inhibitors, which appear to be moving forward rapidly. Nonetheless, after tipranavir (Boehringer Ingelheim's Aptivus®), it is unlikely that another new ARV drug will be licensed before mid-2006 in the US. Of the 32 new ARV drugs now being tested in humans, eight are not moving forward, and at least two others are doubtful (they've been sitting in their current spaces for longer than necessary—in business, this is called 'loss of opportunity'—and there is no clear idea about whether or when they will be moving forward).

Some sponsors of early-phase drugs appear to be vexed by the simple problem of money. Estimates of the cost of bringing a new drug to market range from \$200-400M (not counting the opportunity costs which double that figure); the universities and biotech firms in charge of some of these agents need to find partners, just to keep the drugs where they are.

Table. Antiretroviral Pipeline 2005

	NRTI	NNRTI	Protease Inhibitors	Entry Inhibitors	Integrase Inhibitors	Maturation Inhibitors	Other
Phase I		KP-1212, mutagenic deoxyribo- nucleoside, <i>Koronis</i>		BMS-378806, gp120 blocker, <i>BMS</i>	JTK-303 (GS 9137), <i>Gilead</i> <i>Sciences</i>		Mifepristone, glucocorticoid antagonist, <i>U Pittsburgh</i>
		695634, GSK			L-870812, <i>Merck</i>		BI-201, Tat inhibitor, <i>Biol nvent</i>
		DOT, dioxolane thymidine, <i>U Georgia</i>					
Phase IB / IIA	Racivir (PSI 5004), <i>Pharmasset</i>	TMC-278, diarylpyrimidine (DAPY), <i>T ibotec</i>	640385, GSK	873140, CCR5 antagonist, <i>GSK/ONO</i>		PA-457, Budding inhibitor, <i>Vitex/Panacos</i>	
	SPD-754, Avexa Ltd						
Phase II	Elvucitabine (ACH-126), <i>Achillion</i>	TMC-125 (etravirine), <i>T ibotec/J&J</i>		PRO-542, attachment inhibitor, <i>Progenics</i>			
	Reverset (D-D4FC), Pharmasset/ Incyte			UK-427 (maraviroc), CCR5 antagonist, <i>Pfizer</i>			
	Amdoxovir (DAPD), <i>RFS Pharm</i>			AMD-070, CXCR4 antagonist, <i>Anormed</i>			
				Vicriviroc (SCH 417, SCH D), CCR5 antagonist, <i>Schering Plough</i>			
				TNX-355, anti-CD4 MAb, <i>T anox/Biogen</i>			
Phase III			TMC-114/r, <i>T ibotec/J&J</i>				

<u>Phase I</u>

In Phase I clinical trials, researchers test a new drug or treatment in a small group of people (\sim 20-80) for the first time to evaluate its safety, determine a safe, active range of doses, and identify initial, acute side effects.

Entry Inhibitors

"Entry inhibitors" is a broad category that encompasses attachment, fusion, and the inhibition of co-receptor antagonists. Mechanically, these are separate components unlikely to induce cross-resistance.

BMS-488043, from BMS, is a small molecule that attaches to gp120, causing a conformational change that disrupts the connection to the CD4 receptor (Lin, 2005). 043 will not be moving forward, but its sister BMS-378806, also a gp120 blocker, continues to be tested.

GSK has optioned a CCR5 inhibitor (873140) from Ono that seems to be helped by a ritonavir "boost". CCR5 receptor occupancy seems both high and long, but the clinical significance of this has not been demonstrated (Sparks, Adkinson 2005). As is the case with all three CCR5 inhibitors furthest along, GSK has shown transient dual/mixed tropism switching (Kitrinos 2005).

Integrase Inhibitors

Integrase is the step in HIV's lifecycle where the HIV genome is inserted into the host's DNA, which happens after reverse transcription (see Figure). None of the integrase inhibitors now in the clinic have been reported on. Two recently got into humans, but have since been discontinued (Little 2005). There are at least seven pre-clinical integrase programs in discovery programs around the world. Merck has one—or maybe two—integrase inhibitors in humans that they will be reporting on soon, including L-870812.

Maturation Inhibitors

Maturation, like entry, is a collection of steps, but this time near the end of the replication cycle, including assembly, budding or extrusion (where the CD4 envelope opens and new immature HIV particles begin to leave the cell), and maturation (where the viral proteins are cut by protease and assume their final, infectious state).

The first maturation inhibitor to enter human trials is from Panacos, PA-457. Although they claim an antiviral effect that lasts for ten days after one dose, the clinical impact of this will be determined only after further study (Martin, Li, Martin 2005).

Other Mechanisms

Preliminary studies suggest that mifepristone, a glucocorticoid antagonist, may lower viral load and raise CD4 cells; it is better known as RU-486, and is metabolized through the CYP3A4 pathway; thus, its use will need to be better defined with other medications. Although it is approved for the

medical termination of intrauterine pregnancy, it has not been studied with other drugs or food (Muthumani 2005). ACTG 5200 is a 48-patient randomized, placebo-controlled, phase I/II trial of the anti-HIV activity and safety of mifepristone (here called VGX-410) at three dose levels in HIV-1 infected individuals.

BioInvent has just entered human trials with a Tat inhibitor known as BI-201. It is being looked at in naïve HIV-infected patients. The primary objective is to study safety, tolerability and pharma-cokinetic properties of the candidate drug.

Old Classes, New Drugs

What all new drugs in existing classes are expected to do is to offer some benefit over existing drugs in terms of tolerability, ease of use, side effects, or treatment of resistant HIV strains.

NNRTIs

KP-1212, Koronis' "covert" nucleoside, a perplexing term, has finished Phase I, and will start recruiting for a Phase Ib trial in summer 2005. No consistent toxicities were noted, the pharmacokinetics were as predicted by animal studies, and FDA has given the green light to move forward (Koronis 2005). GSK's nominee, 695634, induces the CYP3A4 pathway – that is, it speeds up the clearance of many other drugs, including HIV drugs, from the body. Rash is a reported side effect; 5/31 persons stopped the drug early in a recent 10-day trial (Persky, Kim 2004). The University of Georgia is the discoverer of another NNRTI, this one a dioxolane thymidine (DOT). DOT has shown anti-HIV activity against many nucleoside-resistant mutants, including the K65R (Chu 2005).

Tibotec has presented a 7-day phase IIA, dose-escalating, placebo-controlled proof-of-principle study, conducted in 47 male antiretroviral-naïve patients. Four doses of TMC278 once daily (in a PEG400 solution) were compared with placebo; the viral load reductions were -1.2 \log_{10} in all TMC278 treatment arms and $-0.002 \log_{10}$ in the placebo group. CD4s rose a median of 55 in 7 days. There was grade 3 nausea reported, and grade 3 lowering of white blood cells and neutrophils in a small number of patients. Mild headache, fatigue, nausea and somnolence were also reported. It has a relatively high genetic barrier for an NNRTI. It is completely cross-resistant to TMC125, another Tibotec NNRTI further along in development (see below). Multinational phase II dose-finding studies are beginning now (de Bethune, Goebel 2005).

NRTIs (nukes)

Pharmasset's racivir seems to be effective against the M184V mutation (seen in 3TC failures). It has shown activity of 2 logs within a triple regimen (Pharmasset 2004). Oddly enough, Avexa's SPD-754, originally from Shire, also purportedly works in the presence of the same resistance mutation. Avexa has a trial designed to look at second line use in the presence of the 184 (Shire 2005). Both companies are also looking at head to heads trials with 3TC.

Phases II & III

In Phase II clinical trials, the study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety. In Phase III studies, the study drug is given to large groups of people (500-1,000+) to confirm its effectiveness, monitor side effects, compare it to an approved standard regimen, and collect information that will allow the drug to be used safely.

Entry Inhibitors

While there is still much to learn about these new compounds, including their impact on HIV tropism switches (from the more normal, less rapidly pathogenic R5/non-syncytium inducing/NSI HIV to the more aggressive, rapidly destructive X4/SI strains), side effects, and the need for boosting with ritonavir, the rapid progress on a number of compounds which inhibit R5 HIV, X4 HIV, or block entry by other mechanisms has the potential to usher in a broad array of potent, new tools for inhibiting HIV.

PRO-542, also known as a recombinant CD4-IgG2 is the latest in the line of soluble CD4 receptors, a group of agents which showed little efficacy when tested in the years before the emergence of HAART, (AIDSMap 2004) and is probably the furthest behind developmentally. PRO-542 binds to HIV's surface at gp120 and blocks attachment and entry of virus into CD4 +cells. At 25 mg, it has a half-life of three days and lowers viral load by half a log for 4-6 weeks post-treatment. PRO-542 will be looked at in salvage patients (Jacobson 2004).

Of the CCR5 inhibitors, Schering's vicriviroc (SCH 417, SCH D) seems especially potent on a per-weight basis. It maintains good bioavailability well above the in vitro IC90 (3.9 ng/mL) even at the low doses being evaluated - between 5 and 15mg. The drug is being studied in experienced patients (clinicaltrials.gov 2004). Virus resistant to SCH 417 has recently been shown to be cross-resistant to other CCR5 inhibitors (Strizki 2005). Like maraviroc and 873140, it has a long half-life and is rapidly absorbed.

Pfizer's maraviroc, formerly UK-427, is effectively doubled in the presence of lopinavir/ritonavir (Kaletra), while exposure is reduced by co-administration of efavirenz. As monotherapy, it lowered viral load in treatment-naïve people by 1.6 log₁₀. No heart-rate (QTc) effects (a la SCH C) have been seen (Muirhead, Westby 2005). The 300 mg dose has been looked at, and an ACTG trial is looking at 150 mg administered once or twice daily (clinicaltrials.gov 2004).

Tanox licensed TNX-355, a monoclonal antibody (designed to compete with CD4-binding antibodies) from Biogen Idec. TNX-355 is a large molecule that requires intravenous infusion, but only once every week or, after eight weeks, every two weeks. TNX-355 is being studied in treatment-experienced persons who have been on at least one failing triple regimen (clinicaltrials.gov 2004).

AMD-070 is a CXCR4 inhibitor, and would seem to be a natural complement to CCR5 inhibitors, for use in treating individuals with mixed-tropic HIV populations, among those with X4 predominance and—if R5 inhibitors induce viral tropic switches—to delay or limit the emergence of X4 HIV. By itself,

AMD-070 would be used in advanced individuals with a mixed or complete X4 HIV population. It has shown preliminary results versus virus with multiple resistance mutations (Schols 2005).

NRTIs

Reverset from Incyte (formerly Pharmasset) is also looking for the anti-184V prize. It is in Phase IIb, although the sponsor has only reported on 16 people so far. It seems to have strong efficacy in persons with the 184V, 41, or 210 RT mutations. Of course, besides who gets there first, price and user-friendliness will play a role if there are several simultaneous post-3TC drugs. And what about the cross resistance between them?

Elvucitabine (Achillion) was in the forefront of the anti-184 drugs (ie, those designed to treat HIV that is resistant to 3TC or FTC due to the 184V mutation in RT). Formerly known as ACH-126, elvucitabine is taken as one pill, once a week. It is being looked at in modestly detectable HIV. The doses used so far have been fairly toxic, and lower doses are being considered (Pottage, 2004).

DAPD (amdoxovir) was looked at in a double blind, placebo controlled study over an optimized background regimen that contained T-20 in all patients. The drug appeared safe but there was no appreciable difference between it and the placebo (Gripshover 2005). Lenticular opacities (eye problems) were seen in animals and Phase I studies. Gilead sold the rights back to the University of Georgia. Further progress of this agent is up to the new guardian, RSF Pharmaceuticals; an ACTG trial is moving forward.

NNRTIs

Etravirine (formerly TMC-125) is another Tibotec agent now in Phase IIb. The two Tibotec NNRTIs under development have overlapping resistance profiles. Etravirine is still in phase IIB dose-finding (400mg or 800 mg BID), while also in a first-NNRTI failure study (at 800 mg BID) (clinicaltrials.gov 2004). Etravirine will share a Phase III study with TMC-114/r, a second investigational agent, hopefully set to begin recruitment in Fall 2005.

TMC-114/r – New PI in Phase III

Tibotec has presented data from 24-week interim analyses of two phase IIB (dose-finding), randomized trials of TMC114/r in patients with 3-class experience and 1 or more primary PI mutations. These analyses showed a mean reduction in plasma HIV RNA of –1.85 log₁₀ in the highest dose group, 600mg/100mg twice daily. Only 11% of participants were female. People were randomized to receive optimized background regimen (OBR) plus one of four doses of TMC114/r or OBR plus investigator-selected control protease inhibitors (PIs).

The interim analysis included a total of 497 patients (Katlama 2005). After 24 weeks, the percentage of participants reaching undetectable virus levels (<50 copies/ml) ranged from 30% to 47% in the TMC114/r arms, compared with 10% in the control arm. 67% of those who were also taking T-20 went below 50. The most common adverse events were headache, nausea, diarrhea, and fatigue, although up to 90% of participants reported some sort of side effects, 25% of them grades 3 or 4.

These studies will continue to 96 weeks. Based on these 24-week results, the selected dose for treatment-experienced people in phase III trials will be TMC114/r 600mg/100mg twice daily; the trials are set to begin in summer 2005.

Multi-Experimental Agent Trials (MEAT)

While drug studies for healthier patients usually utilize the very newest drugs in early development, later stage patients are often left out.

Since 1999, FDA has talked openly about how to design a good "heavily pretreated patient" study. They have let it be known that trials with multi-experimental agents are viable for registration.

As a result of the community and FDA's focusing on experienced patients, drugs such as Kaletra (lopinavir/ritonavir), Viread (tenofovir DF), Fuzeon (T-20) and tipranavir/R (Aptiva®) were all studied in pre-treated, sometimes salvage therapy populations, and these drugs were actually approved first for use in pre-treated individuals.

A combination trial can answer 'Are these two (or more) experimental agents together useful?' And it would prevent virtual monotherapy for people in salvage. Variables that need to be addressed include resistance and cross-resistance, choice of OBR, the use/availability of newer drugs not directly being studied, and drug interaction/PK studies.

Ever since the community first proposed the ARISTO ['A RandomIzed study of Salvage Treatment Options'] study in 1999, in which three experimental agents would be evaluated together (James 1999), there has been interest in studies utilizing several experimental agents together. 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. Recently, the FDA clarified once again its willingness to countenance the implementation of such studies (Struble 2005).

The Future of Expanded Access

For a decade, since the introduction of HAART in 1996, sponsors have kept their expanded access programs (EAPs) small and late. In earlier years, Burroughs Wellcome provided 5,000 late-stage AIDS patients with AZT before approval in 1987. Bristol-Myers provided ddl 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. Even then, Roche was always a grudging and late-coming provider of access to, for example, ddC for about 5,000 people and later saquinavir to an equivalent number. Sponsors claimed the complexity of protease inhibitor manufacturing processes limited their ability to distribute PIs through EAPs. Indeed, there were

ethically challenging programs such as lotteries for access to the first PIs. More recent EAPs for drugs such as T-20 (Roche), atazanavir (BMS), and tipranavir/R have hardly been worthy of the name.

Can expanded access be rejuvenated as a more equitable, broadly based pre-approval program which can provide access to experimental therapies for all individuals who need them but cannot access the controlled clinical trials, or are ineligible?

Summary

Of the 24 anti-HIV agents continuing in the clinical pipeline, up to twenty may likely make it through to FDA review within the next four to six years (see Table, page 5). Some companies like Anormed have announced they will not be moving forward, in this case, with their CXCR4 inhibitor AMD3100. Others companies, like BI with MIV-310, have sold the agent back to their originator. And at least two are like Advanced Life Science's Calanolide A, hovering for much too long in the same place. Even their press releases are getting old.

On the other hand, if no new bad news for the entry class comes out, we may see a broadening of licensed anti-HIV therapy approaches toward the very earliest stages of the HIV life cycle—before its entry into cells—to intermediate stages such as integration and later stages such as assembly, budding, and maturation inhibition.

The obstacles to a better future for people with HIV are clear, however. 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 treatments. There are many major players in the drug development process. The pharmaceutical industry is pre-eminent among them. Nonetheless, continued vigilance, activism, and informed advocacy are crucial to fostering more enlightened drug development, approval, and post-marketing access and availability processes.

References

Adkison K, Shachoy-Clark A, Fang L, et al. Abstr 664. The Pharmacokinetic Interaction between the CCR5 Antagonist 873140 and Lopinavir/Ritonavir in Healthy Subjects. 12th CROI. Feb 22-25, 2005. Boston, USA.

AIDSMap. PRO-542, updated 10 December 2004. http://www.aidsmap.com/en/docs/15804674-D998-4B2F-811F-6CED0AC33F93.asp.

Amdoxovir (DAPD), http://www.aidsmeds.com/drugs/amdoxovir.htm.

Bethell RC, Collins P. Genotypic and Phenotypic Analysis of HIV-1 Isolates from Patients after 10 Days Monother-apy with SPD754. H-206. 44th ICAAC. October 30–November 2, 2004. Washington, DC.

Bethell RC, de Rooj ER, Smolders KGM, et al. Comparison of the In Vitro Mitochondrial Toxic-ity of SPD754 in HepG2 Cells with Nine Other Nucleoside Reverse Transcriptase Inhibitors. H-207. 44th ICAAC. October 30 – November 2, 2004. Washington, DC.

Bethell et al, The XV International AIDS Conference, 2004, Bangkok, Thailand. WePeA5642de Béthune M-P, Andries K, Azijn H, et al.TMC278, a New Potent NNRTI, with an Increased Barrier to Resistance and Good Pharmacokinetic Profile. Abstr 556. 12th CROI. Feb 22-25, 2005. Boston, USA.

Camp R. Letter on pharmacokinetic (PK) issues and drug-drug interaction studies to Debra B. Birnkrant, Division of Anti-Viral Drug Products, Center for Drug Evaluation and Research, Office of New Drugs, FDA, 2004. http://www.aidsinfonyc.org/tag/activism/fdaCDERltr.html.

Chen B, Vogan EM, Gong H, Skehel JJ, Wiley DC, Harrison SC. Structure of an unliganded simian immunodeficiency virus gp120 core. Nature 433, 834–841 (2005); doi:10.1038/nature03327

Chu CK, Yadav V, Rapp K, Chong Y, and Schinazi R. Dioxolane Thymine Nucleoside Is Active against a Variety of NRTI-resistant Mutants. Abstr 554. 12th CROI. Feb 22-25, 2005. Boston, USA.

Demarest J, Sparks S, Watson C, et al. H-211. Prolonged and Unique Binding of a Novel CCR5 An-tagonist, 873140. 44th ICAAC • Washington, DC • October 30–November 2, 2004.

Department of Health & Human Services (DHHS) Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. 7 April 2005. http://www.aidsinfo.nih.gov/guidelines/adult/AA_040705.pdf.

Egbertson M, Langford M, Melamed J, et al. A Potent and Orally Active HIV Integrase Inhibitor and Pre-Clinical Candidate. F-484. 44th ICAAC. October 30–November 2, 2004. Washington, DC.

Elford HL, Lee R, Gallichio VS, et al. The Benefit of Inclusion of Ribonucleotide Reduc-tase (RR) Inhibitors Didox (DX) and Trimidox (TX) in Retrovirus Treatment. H-208. 44th ICAAC. October 30–November 2, 2004. Washington, DC.

Ford S, Reddy S, Anderson M, Murray S, Ng-Cashin J, Johnson M. 640385, a Novel HIV-1 Protease Inhibitor: Safety and Pharmacokinetics following Repeat Administration with and without Ritonavir in Healthy Subjects. Abstr 563. 12th CROI. Feb 22-25, 2005. Boston, USA.

Fransen S, Gupta S, Paxinos E, et al. Integrase Inhibitor Susceptibility Can Be Measured Using Recombinant Viruses that Express Patient Virus Integrase Alone, or in Combination with Protease and Reverse Transcriptase. Abstr 725. 12th CROI. Feb 22-25, 2005. Boston, USA.

Franti M, Ramos L, Maloveste S, et al. In vivo control of HIV-1 replication with PRO 140, a humanized monoclonal antibody to CCR5. Abstr WeOrA1230. The XV International AIDS Conference, 2004, Bangkok, Thailand.

Goebel F, Yakovlev A, Pozniak A, et al. TMC278: Potent Anti-HIV Activity in Antiretroviral Therapy-naïve Patients. Abstr 160. 12th CROI. Feb 22-25, 2005. Boston, USA.

Gripshover B, Santana J, Ribaudo H, et al. A Randomized, Placebo-controlled Trial of Amdoxovir vs Placebo with Enfuvirtide plus Optimized Background Therapy for HIV-infected Subjects Failing Current Therapy (AACTG 5118). Abstr 553. 12th CROI. Feb 22-25, 2005. Boston, USA.

Holdich et al. Abstr TuPeB4625. The XV International AIDS Conference, 2004. Bangkok, Thailand.

Jacobson JM, Israel RJ, Lowy I, et al. Treatment of Advanced Human Immunodeficiency Virus Type 1 Disease with the Viral Entry Inhibitor PRO-542. Antimicrobial Agents and Chemotherapy, February 2004, p. 423-429, Vol. 48, No. 2.

James JS. Activism Today: The Coalition for Salvage Therapy. Interview with Linda Grinberg. AIDS Treatment News 330, 5 November 1999. http://www.aids.org/atn/a-330-04.html.

Katlama C, Berger D, Bellos N, et al. Efficacy of TMC114/r in 3-Class Experienced Patients with Limited Treatment Options: 24-Week Planned Interim Analysis of 2 96-week Multinational Dose-finding Trials. Abstr 164LB. 12th CROI. Feb 22-25, 2005. Boston, USA

Kim Y, Symonds W, Steel H, et al. Safety and Pharmacokinetics (PK) of 695634 following Repeat Oral Dose Administration to Healthy Subjects. A-23-2004. 44th ICAAC. Washington, DC. October 30–November 2, 2004.

Kitrinos K, LaBranche C, Stanhope M, Madsen H, Demarest J. Clonal analysis detects pre-existing R5X4-tropic virus in patient demonstrating population-level tropism shift on 873140 monotherapy. Abstr 61, 14th International HIV Drug Resistance Workshop, 7-11 June 2005. Quebec City, Canada.

LaBranche CC, Davison D, Ferris RG, et al. Studies with 873140, a novel CCR5 antagonist, demonstrate synergy with enfuvirtide and potent inhibition of enfuvirtide-resistant R5-tropic HIV-1. Abstr 66, 14th International HIV Drug Resistance Workshop, 7-11 June 2005. Quebec City, Canada.

Li F, Zoumplis D, Matallana C, et al. The Determinants of Activity of the HIV-1 Maturation Inhibitor PA-457 Map to Residues Flanking the Gag CA-SP1 Cleavage Site. Abstr 256. 12th CROI. Feb 22-25, 2005. Boston, USA.

Lin PF, Ho H, Fan L, et al. Inhibition Mechanism of Small-molecule HIV-1 Attachment Inhibitors. Abstr 544. 12th CROI. Feb 22-25, 2005. Boston, USA.

Little S, Drusano G, Schooley R, et al. Antiretroviral Effect of L-000870810, a Novel HIV-1 Integrase Inhibitor, in HIV-1-infected Patients. Abstr 161. 12th CROI. Feb 22-25, 2005. Boston, USA.

Martin D, Ballow C, Doto J, Blum R, Wild C, and Allaway G. The Safety, Tolerability, and Pharmacokinetics of Multiple Oral Doses of PA-457, the First-in-class HIV Maturation Inhibitor, in Healthy Volunteers. Abstr 551. 12th CROI. Feb 22-25, 2005. Boston, USA.

Martin D, Jacobson J, Schurmann D, et al. PA-457, the First-in-class Maturation Inhibitor, Exhibits Antiviral Activity following a Single Oral Dose in HIV-1-infected Patients. Abstr 159. 12th CROI. Feb 22-25, 2005. Boston, USA

Mascolini M, http://www.natap.org/2001/jan/antiviral panel011501.htm.

McSharry JJ, Deziel M, Louie A, et al. Pharmacodynamics of 873140, an Inhibitor of CCR5, in an In Vitro Hollow Fiber Model. H-212. 44th ICAAC. October 30–November 2, 2004. Washington, DC.

Anti-HIV Activity and Safety of 3 Different Doses of Mifepristone in HIV Infected People, http://www.clinicaltrials.gov/ct/show/NCT00099645?order=3

Moore RD, Keruly JC, Gebo KA, Lucas GM. An improvement in virologic response to highly active antiretroviral therapy in clinical practice from 1996 through 2002. J Acquir Immune Defic Syndr 1 June 2005;39(2):195-198.

Muirhead G, Pozniak A, Gazzard B, et al. A Novel Probe Drug Interaction Study to Investigate the Effect of Selected ARV Combinations on the Pharmacokinetics of a Single Oral Dose of UK-427,857 in HIV + ve Subjects. Abstr 663. 12th CROI. Feb 22-25, 2005. Boston, USA.

Murphy R, et al. Abstr MoOrB1056. The XV International AIDS Conference, 2004, Bangkok, Thailand.

Muthumani K, Boyer J, Choo A, et al. Therapeutic Inhibition of SIV Replication in Macaques by GR Blockade and Implications for Therapy of HIV-1. Abstr 158. 12th CROI. Feb 22-25, 2005. Boston, USA.

Nakata H, Koh Y, Maeda K, et al. Greater Synergistic Anti-HIV Effects upon Combinations of a CCR5 inhibitor AK602/ONO4128/GW873140 with CXCR4 Inhibitors than with Other Anti-HIV Drugs. Abstr 543. 12th CROI. Feb 22-25, 2005. Boston, USA.

NIH, NIAID, TNX-355 with Optimized Background Therapy (OBT) in Treatment-Experienced Subjects with HIV-1, http://www.clinicaltrials.gov/ct/show/NCT00089700?order=1.

NIH, NIAID, clinicaltrials.gov, Safety and Effectiveness of the Oral HIV Entry Inhibitor SCH 417690 in HIV Infected Patients http://www.clinicaltrials.gov/ct/show/NCT00082498?order=1.

Persky AM, Moore KHP, Kim YH, Symonds W, Denning J, Frye RF. Effect of 695634, a Next Generation NNRTI, on Cytochrome P450 (CYP) Probe Substrates. A-461-2004. 44th ICAAC. October 30–November 2, 2004. Washington, DC.

Pesano R, Piraino S, Hawley P, et al. 24 Week Safety, Tolerability, and Efficacy of Capravirine as Add-on Therapy to Nelfinavir and 2 Nucleoside Reverse Transcriptase Inhibitors in Patients Failing a Non-nucleoside Reverse Transcriptase Inhibitor-based Regimen. Abstr 555. 12th CROI. Feb 22-25, 2005. Boston, USA.

Pharmasset Press Releases. Results of Phase IIa Study Show That Reverset Has Potential to Reduce HIV Viral Load in Treatment-Experienced Patients, Oct. 31, 2004, Washington DC. Pharmasset Initiates Racivir Phase II HIV Study, November 10, 2004. http://www.pharmasset.com/go/67e4e309-7a73-1157-b59d-d5b376410482?itemId=1ca4b1d1-333c-1149-96bb-f1b6f686db51.

Pottage J, hivpharmacology.com, 5th Intl Pharmacology Workshop. Abstr 38. April 1-3, 2004. Rome, Italy.

http://www.investor.incyte.com/phoenix.zhtml?c=69764&p=IROL-NewsText&t=Regular&id=638154&

Randolph JT, Huang P, Flentge C, et al. A-681799, a Novel HIV Protease Inhibitor. F-485. 44th ICAAC. October 30–November 2, 2004. Washington, DC.

Roschke V, Clark S, Branco L, et al. H-213 Characterization of a Panel of Novel Human Mono-clonal Antibodies that Specifically Antagonize CCR5 and Block HIV Entry. 44th ICAAC. October 30–November 2, 2004. Washington, DC.

Schols D, Vermeire K, Fransen S, et al. Multi-drug Resistant HIV-1 Is Sensitive to Inhibition by Chemokine Receptor Antagonists. Abstr 545. 12th CROI. Feb 22-25, 2005. Boston, USA.

Shire/Avexa Press release, HIV compound SPD754 out-licensed to anti-infectives specialist, Avexa Ltd, http://www.shire.com/shirepharma/NewsAndMedia/PressReleases/showShirePress.jsp?ref=378, 17 January 2005.

Sparks S, Adkison K, Shachoy-Clark A, Piscitelli S, Demarest J. Prolonged Duration of CCR5 Occupancy by 873140 in HIV-negative and HIV-positive Subjects. Abstr 77. 12th CROI. Feb 22-25, 2005. Boston, USA.

Strizki JM, Wojcik L, Marozsan AJ, et al. Properties of in vitro generated HIV-1 variants resistant to the CCR5 Antagonists SCH 351125 and SCH 417690 (Vicriviroc). Abstr 59, 14th International HIV Drug Resistance Workshop. June 7-11, 2005. Quebec City, Canada. Struble K, Murray J, Cheng B, Gegeny T, Miller V, Gulick R. Antiretroviral therapies for treatment-experienced patients: current status and research challenges, AIDS 2005, 19:747-756.

The Center for AIDS, RITA (Research Initiative Treatment Action!), Vol 10 No 1, Summer 2004, http://www.centerforaids.org.

TMC125, http://www.clinicaltrials.gov/ct/show/NCT00081978?order=1.

Westby M, Smith-Burchnell C, Hamilton D, et al. Structurally related HIV co-receptor antagonists bind to similar regions of CCR5 but have differential activities against UK-427,857-resistant primary isolates. Abstr 96. 12th CROI. February 22-25, 2005. Boston, USA.

Youle M, et al. Letter, The Lancet, Vol 364, N 9439, 18 September 2004.

Wai JS, Kim BY, Fischer TE, et al. Dihydroxypyridopyrazine-1,6-dione HIV-1 Integrase Inhibitors. F-483. 44th ICAAC. October 30–November 2, 2004. Washington, DC.

Westby M, Mori J, Smith-Burchnell C, et al. Maraviroc (MVC, UK-427,857)-resistant HIV-1 variants, selected by serial passage, are sensitive to CCR5 antagonists (GW873140, Schering-C, Schering-D) and T-20 (enfuvirtide). Abstr 6. 14th International HIV Drug Resistance Workshop, 7-11 June 2005. Quebec City, Canada.

Zhang M, Dimitrov DS. H-214 Inhibition of HIV-1 Entry: Broadly HIV-1 Neu-tralizing Human Monoclonal Antibodies and their Derivatives. 44th ICAAC. October 30–November 2, 2004. Washington, DC.

Immune-Based Therapies and Preventive Technologies Pipeline by Richard Jefferys

The Current Landscape

The development of immune-based HIV therapies, preventive HIV vaccines, and microbicides is hampered by a common problem: the lack of any effective precedent. All three fields are currently attempting to build on a barren landscape—a challenge not faced by developers of new antiretroviral, hepatitis C, and TB treatments. This makes investment in this research high-risk and highly dependent on public funding. Many of the products in the pipeline are the fruits of collaborations between academic and/or government investigators, small companies, and non-profit organizations. Even if proven successful, obtaining regulatory approval and scaling up manufacturing to allow widespread distribution will likely depend on additional investments, the prospects for which are uncertain. In short, the path through these particular pipelines is tortuous and difficult. Additionally, preventive vaccines and microbicides must confront a problem also faced by new treatments for TB: the vast majority of the potential market for these products is primarily in the developing world where people have the least ability to pay. Again, this puts the onus on public-private collaborations to walk a landscape where most major pharmaceutical companies fear to tread.

Preventive Technologies: Vaccines

Over the last five years, the once-dry preventive vaccine pipeline has begun to fill with new candidates. This upsurge can be traced to improvements in techniques for inducing T-cell (also known as cell-mediated) immune responses. Initial efforts to develop an HIV vaccine focused primarily on candidates designed to induce neutralizing antibodies against the virus. These efforts, however, were severely compromised by the discovery that, while HIV viruses grown in the lab could be easily neutralized, viruses taken from infected people (called primary isolates) are highly resistant to antibody-mediated neutralization. The relevance of these observations was confirmed by the failure of an early antibody-based vaccine candidate (AIDSVAX) to protect against HIV infection in two large efficacy trials (Flynn 2005; Pitisutithum 2004).

While researchers continue to work on strategies for inducing neutralizing antibodies against HIV, only a minority of the vaccines currently in human trials are antibody-based. Instead, the leading candidates have drawn on evidence that T-cell responses may play an important role in controlling HIV infection (Pantaleo 2004). T-cell responses are comprised of both CD4 "helper" and CD8 "killer" T cells. The ability of scientists to dissect T-cell responses has improved vastly over recent years due to new technologies that allow the numbers, specificity (i.e., the pathogen they are targeting), and functional properties of CD4 and CD8 T cells to be evaluated. Most researchers believe it is unlikely that a T-cell–based vaccine will completely protect against HIV infection, but there is some optimism that it could slow or prevent disease progression in an immunized individual who subsequently becomes HIV-infected. Also, if vaccination could reduce post-infection viral load, the risk of onward transmission of the virus might also be reduced.

The leading vaccine strategies for inducing HIV-specific T-cell responses involve the use of naked DNA (genetic code engineered to make selected HIV proteins when delivered into the body) and viral vectors (harmless viruses altered so that they carry the genetic code for making selected HIV proteins when delivered into the body). Other approaches being investigated in human clinical trials include lipopeptide and whole protein vaccines.

Desired Elements

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 clades
- Long-lasting immunity
- Safe
- Easy to deliver (e.g., a single shot)
- Cheap
- Easy to manufacture on a large scale
- Easy to ship and distribute globally

A Note on Antigens and Clades

An important aspect of vaccine design is deciding which parts of HIV (in immunological parlance, HIV "antigens") 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 is 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 their decision on the relative conservation of these genes across different HIV clades. Clades 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 clade B. Many viruses found in Africa are also similar, but show distinct genetic differences from HIV clade B and are therefore classified as belonging to different clades (clades A, C and D are the most common in Africa). Mixes between different clades are called circulating recombinant forms (CRFs), for example the prevalent HIV in Thailand was once classified as belonging to clade E but is now designated as a mix between clades 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 clade may fail to recognize viruses from other clades. Hence Merck's focus on genes from HIV that are very similar from clade to clade (in general, HIV's *env* gene varies the most while *gag* is the most conserved). While initially most vaccine candidates were based on HIV clade B, an increasing number are now including HIV components from alternative or multiple clades.

PRODUCT TYPE MANUFACTURER **STATUS** ALVAC vCP1521 Phase III Canarypox vector Aventis Pasteur AIDSVAX B/E (booster only) Gp120 envelope recombinant protein VaxGen Phase III MRKAd5 Adenovirus serotype 5 vector Merck Phase II b containing gag/pol/nef genes from HIV-1 clade B LIPO-5 5 lipopeptides ANRS; Aventis Phase II containing CTL epitopes (on hold (from gag, po/, and nef) due to toxicity) GTU-Multi-HIV DNA vaccine containing nef, rev, tat, FIT Biotech Phase I/II gag, pol, env, and CTL epitopes Phase I/II pHIS-HIV-B DNA vaccine + fowlpox boost University of New South Wales, Australia, Virax rFPV-HIV-B containing gag, rev, tat, vpu, and truncated env genes from HIV-1 clade B ADMVA MVA vector containing env/gag-po/, Aaron Diamond AIDS Research Phase I and nef-tat genes from HIV-1 clade C Center (ADARC), IAVI, IDT GlaxoSmithKline Phase GSK Protein HV Vaccine Recombinant Tat, Nef, and gp120 proteins in ASO2A adjuvant VRC-HIVADV014-00-VP Adenovirus serotype 5 vector NIH Vaccine Research Center Phase I containing gag/po/ genes from (both alone and HIV-1 clade B and env genes from as a booster) clades A. B. and C AlphaVax AdVax 101 (VEE) Venezuelan Equine Encephalitis virus Phase I vector containing the gag gene from HIV-1 clade C VRC-HIVDNA016-00-VP DNA vaccine containing gag, po/, and NIH Vaccine Research Center Phase I nef genes from HIV-1 clade B, and env genes from clades A, B, and C MVA and fowlpox vectors encoding Phase TBC-M358 (MVA) NIAID, Therion TBC-M335 (MVA) env. gag. tat. rev. nef. and TBC-F357 (FPV) reverse transcriptase genes TBC-F349 (FPV) from HIV-1 clade B LIPO-4T (LPHIV-1) 4 lipopeptides containing CTL epitopes ANRS. Biovector SA Phase I (from gag, po/-RT, po/, and nef) Phase LFn-p24 Anthrax-derived polypeptide LFn AVANT, NIAID, WRAIR Gag p24 protein

Table 1. Preventive Vaccines Pipeline

PRODUCT	ТҮРЕ	MANUFACTURER	STATUS
HIV CTL MEP	DNA vaccine containing CTL epitopes from <i>env</i> or <i>gag</i>	NIAID, Wyeth	Phasel
DNA + Protein Vaccine Combination	DNA vaccine containing a <i>gag</i> gene (from HIV-1 clade C) and 5 <i>env</i> genes (from clades A, C, and E + two from clade B), plus a protein boost using recombinant gp120 proteins from the same 5 isolates that supplied the <i>env</i> genes for the DNA component	University of Massachusetts Medical School, Advanced BioScience Laboratories, Inc.	Phase I
tgAAC09 AAV	Adeno-associated virus vector containing <i>gag</i> , protease, and reverse transcriptase genes from HIV-1 clade C	Targeted Genetics, IAVI	Phasel
ADVAX DNA	DNA vaccine containing <i>gag, env, pol, nef,</i> and <i>tat</i> genes from HIV-1 clade C	IAVI, ADARC, Vical	Phase I
DNA/PLG Oligomeric gp140/MF59	DNA vaccine containing <i>gag</i> and <i>env</i> genes from HIV-1 clade B, plus a protein boost containing a gp140 protein also from clade B	Chiron	Phase I
VRC-HIVDNA-009-00-VP	DNA vaccine containing <i>gag, pol,</i> and <i>nef</i> genes from HIV-1 clade B, and <i>env</i> genes from clades 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 <i>env</i> genes	St. Jude's Children's Hospital	Phase I
ISS P-001	Recombinant Tat protein from HIV-1 clade B	ISS, Excell	Phase I
EP HIV-1090 DNA	DNA vaccine containing 21 CTL epitopes from <i>gag, pol, env, nef, rev,</i> and <i>vpr</i> (HIV-1 clade B)	NIAID, Epimmune	Phase I

Table 1. Preventive Vaccines Pipeline (Cont.)

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 vaccine 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 only around 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 response rate (known as the vaccine's immunogenicity), but none have

proved successful. ALVAC version vCP1521 (which encodes HIV-1 CRF01_AE *env* and clade 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. Results should be available within the next five years. Many leading HIV vaccine scientists have harshly criticized the planning and design of this trial, as has TAG (Burton 2004; Jefferys 2004).

AIDSVAX: A Dishonorable Mention

In the early years of HIV vaccine development, when it was thought that antibodies to the viral envelope protein gp120 might be successful, several companies made constructs using recombinant gp120 proteins. Among them is the AIDSVAX vaccine (manufactured by a company called VaxGen) that failed to protect against HIV infection or slow disease progression in two phase III trials. Initial claims by VaxGen that the vaccine had shown some protection in people from particular ethnic backgrounds were quickly revealed to be spurious (Follman 2004). Although the trial results indicate that AIDSVAX should have been flushed from the vaccine pipeline, it is still being used as a booster in the Thai ALVAC trial mentioned above.

Adenovirus-Based Vaccines

Merck created a splash in 2001 when it announced the launch of a clinical development program for an HIV vaccine candidate based on two platforms: naked DNA and a viral vector using adenovirus serotype 5 (Ad5). Ad5 was chosen in part due to its salutary ability to target dendritic cells, the initiators of T-cell responses. The original plan, based on promising immunogenicity studies in macaques, was to utilize the DNA vaccine as a "prime" (to generate low-level HIVspecific T-cell responses) followed by the Ad5 vaccine as a "boost" (to raise the HIV-specific T-cell responses to much higher levels). Human trials have since shown that the DNA vaccine is only marginally immunogenic, leading Merck to focus on the Ad5 construct. The data to date on Ad5 (still unpublished) appear to be highly promising, with one very significant caveat. The good news is that Ad5 can induce HIV-specific CD8 T-cell responses in up to 60–70% of recipients, a far superior showing compared to the previous best achieved by ALVAC (Isaacs 2004). The bad news is that this robust immunogenicity is seen only in people that lack significant levels of neutralizing antibodies against Ad5 (in its natural form, Ad5 is a common cause of severe colds and many people have been exposed to it). It's estimated that about a third of the North American population has high levels (a titer of over 200) of neutralizing antibodies against Ad5; in the developing world the proportion approaches 90% (Kostense 2004). In such individuals, Ad5 is essentially about as immunogenic as ALVAC.

As a result of this dilemma, Merck is currently collaborating with the HIV Vaccine Trials Network (HVTN) on a phase IIb "proof of concept" efficacy trial that restricts enrollment to individuals with low levels of anti-Ad5 antibodies. The primary goal of the study is to evaluate whether the HIV-specific T-cell responses induced by the vaccine (which encodes the *gag*, *pol*, and *nef* genes from HIV clade B) can offer protection against HIV infection and/or disease progression. Results are expected by 2007. Because so many current candidates aim to induce T-cell responses, the study is addressing a critical question for the future of HIV vaccine research; if the results are positive, alternative versions of the vaccine will have to be developed in order to circumvent the neutralizing

antibody problem. Merck is looking at less common Ad5 serotypes such as 11 and 35. Work is also underway to determine whether the Ad5 vaccine can be modified to evade preexisting antibody responses by altering the Ad5 hexon protein, which is the major target of these antibodies (Sumida 2005).

The NIH's Vaccine Research Center (VRC) has developed another Ad5 candidate, which is in human trials. VRC is testing this vaccine both alone and as a booster to its DNA vaccine. VRC's long-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. However, as with the Merck construct, the issue of pre-existing antibodies to Ad5 will need to be addressed.

Lipopeptides

Lipopeptides comprise synthetic fragments of viral proteins associated with lipids that facilitate the induction of T-cell immune responses. Lipopeptide vaccines have induced HIV-specific CD8 T-cell responses in around 50% of recipients (Salmon-Ceron 2002). 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 studies are currently on hold after a serious adverse event (spinal cord inflammation) in a trial participant.

The Travails of MVA

Modified Vaccinia Virus Ankara strain (MVA) is an attenuated, nonpathogenic derivative of the cowpox virus. An MVA-based HIV vaccine candidate designed by Andrew *Mc*Michael and Tom Hanke from Oxford University has undergone extensive human testing with the support of the International AIDS Vaccine Initiative (IAVI). Unfortunately, the 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. Two other MVA-based HIV vaccine candidates (one manufactured by Therion and the other developed by the Aaron Diamond AIDS Research Center) remain in human studies, but it is unclear whether they will prove more immunogenic. The problem with MVA may be its large size; immune responses targeting the vector appear to dominate at the expense of responses targeting the HIV components that the vector encodes (Harrer 2004).

A Multitude of DNAs

DNA vaccines are perhaps the simplest, cheapest approach for 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 (that is difficult and painful to inject) at doses much above 5 mg. 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 cytokines like IL-2, IL-12, or IL-15) to the DNA vaccine that may boost the T-cell response. (For a detailed review of DNA vaccine development in HIV, see Giri 2004.)

Recombinant Proteins

Shortly 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. Jaded observers of the field rapidly noticed 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 developing 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 vaccine-induced CD8 T cells were detected (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 a monomeric gp120 protein). 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) are using recombinant gp120 proteins from multiple clades (A, C, E, and two from B) as a booster following a DNA vaccine encoding the same *env* genes along with HIV clade B *gag*. The approach, based on unpublished animal data, suggests that immunization with gp120 proteins from multiple clades may induce qualitatively superior antibody responses compared to those induced by gp120 from a single clade.

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 is dependent on adenovirus for replication; 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 the episomes of cells without integration. Immunogenicity results in macaques were impressive, showing a robust, dose-dependent induction of HIV-specific T-cell responses and anti-Gag antibodies (Schulz 2004). A phase I human trial began in Germany at the end of 2003, and results are anticipated by mid-2005.

Venezuelan Equine Encephalitis Virus (VEE)

Originally developed by the U.S. military as a potential biological weapon, an attenuated form of VEE is in testing as a potential HIV vaccine vector under the aegis of the biotech company AlphaVax and NIH (early work on the vector was sponsored by IAVI but they recently ended their relationship with AlphaVax). VEE belongs to a family known as alphaviruses and, like adenovirus, targets dendritic cells. Only limited immunogencity data are available from macaques (Davis 2000); human data from a phase I trial initiated in South Africa in 2002 are pending.

Preventive Technologies: Microbicides

Microbicides are substances that aim to prevent HIV infection (and possibly other STDs) by being applied topically to the vaginal or rectal surface prior to sex. One major advantage to such an intervention, if one could be successfully developed, is that it 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 have recently got underway.

Desired Elements

As outlined in a recent review, 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 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) that can facilitate the slow release of a microbicide over a period of days or months (Woolfson 2000).
PRODUCT	ТҮРЕ	MANUFACTURER	STATUS
Carraguard®	Adsorption inhibitor	Population Council	Phase III
Cellulose sulfate (Ushercell®)	Adsorption inhibitor	CONRAD/Polydex Pharmaceuticals Limited	Phase III
PRO 2000/5 Gel	Adsorption inhibitor	Indevus Pharmaceutical, Inc.	Phase III, Phase II/Ib (with BufferGel), Phase II (with tenofovir)
Savvy (C31G)	Surfactant	Biosyn, Inc.	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 (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-benzenedicarboxylate (cellulose acetate/CAP)	Adsorption inhibitor	Aaron Diamond AIDS Research Center	Phasel
Lime Juice	Acid-buffering agent	University of Melbourne	Phase I
TMC120	Reverse transcriptase inhibitor	International Partnership for Microbicides (IPM)	PhaseI
UC-781	Reverse transcriptase inhibitor	Biosyn, Inc.	Phase I
VivaGel (SPL7013 gel)	Entry/fusion inhibitor	Starpharma Ltd.	Phase I

Table 2. Microbicides Pipeline

The microbicides that have advanced into efficacy trials fall into the following categories:

Surfactants

Surfactants are detergent-like chemicals that disrupt the lipid membranes of cells and the envelope of HIV. 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, but results showed that it marginally increased the risk of HIV infection (Van Damme 2002), likely due 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 by the company Biosyn (Krebs 2000); SAVVY is currently undergoing evaluation in a phase III efficacy trial in West Africa.

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

In earlier phases of human trials are a number of microbicides with direct antiretroviral effects mediated by blocking viral fusion with, or entry into, target cells. There are also several reverse transcriptase inhibitors, including a gel form of the drug tenofovir that is currently in phase II trials (alone and in combination with PRO2000).

Preventive Technologies: Pre-Exposure Prophylaxis (PrEP)

Table 3. Pre-Exposure Prophylaxis (PrEP) Pipeline

PRODUCT	ТҮРЕ	MANUFACTURER	STATUS
Tenofovir (Viread, TDF)	Reverse transcriptase inhibitor	Gilead Sciences, Inc.	Phase II

PrEP is the moniker given to drug therapies that may prevent HIV infection when taken prior to exposure. Currently there is only one candidate 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 for Disease Control, two by Family Health International and the Bill & Melinda Gates Foundation). Recent criticisms of the ethics of these trials have led to the suspension of a study site

in Cameroon and the termination of a proposed study among sex workers in Cambodia. A number of issues have been 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, provision of clean needles to intravenous drug users, plans for condom provision to participants and provision of care for participants that seroconvert and/or experience tenofovir-related toxicities. Discussions among the various stakeholders are now occurring in the hopes that these issues can be addressed.

Immune-Based Therapies

Despite more than two decades of research, there is as yet no approved immune-based therapy (IBT) for HIV infection, and while antiretrovirals continue to course through the developmental pipeline, relatively few potential immunologic interventions are dripping their way toward efficacy trials. This imbalance is partly due to an incomplete understanding of HIV's effects on the human immune system compared to our detailed knowledge of the viral life cycle. Absent this information, targets for IBTs are typically based on theories regarding pathogenesis and thus are susceptible to failure if a particular theory turns out to be incorrect. In contrast, a new antiretroviral compound can be targeted to a well-understood step in the HIV replication process. In addition, several IBTs (including Jonas Salk's ill-starred therapeutic vaccine candidate, Remune, and the bone marrow stimulant GM-CSF) have progressed to phase III efficacy trials but have failed to show clinical benefit (Kahn 2000; Angel 2000), making industry leery of pursuing compounds that risk a similar fate. It is also difficult to assess the prospective market for IBT, given that none are available, while there are years of accumulated data on the sales of antiretroviral drugs.

Desired Elements

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 delayed, or allowed prolonged interruptions of, HAART could potentially reduce both the cost and toxicity of drug therapy. Recently, 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 Vaccines

The advent of HAART has 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. As with preventive vaccines, the field has been aided by improved tools for evaluating the functional properties of HIV-specific T cells. These tools have identified a number of properties that are associated with control of HIV viral load such as IL-2 production and proliferation (Pantaleo 2004; Boritz 2004; Migueles 2002), but it remains to be seen whether the induction of these T-cell responses by vaccination will prove beneficial. The primary goal of therapeutic immunization is to maintain better control of viral

Table 4. Therpeautic Vaccines Pipeline

PRODUCT	ТҮРЕ	MANUFACTURER	STATUS
ALVAC (vCP1452)	Canarypox vector encoding <i>env, gag,</i> the protease-encoding portion of the <i>pol</i> gene and CTL epitopes from the <i>nef</i> and <i>pol</i> 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 <i>gag, pol, nef,</i> and multiclade (A, B, and C) <i>env</i> genes	VRC/NIAID	Phase I
MVA-BN-nef	MVA vector encoding clade 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 encoding gag	Merck	Phase I/II
Autologous dendritic cells pulsed w/ALVAC		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 <i>gag</i> and multiple CTL epitopes	Cobra Pharmaceuticals, Impfstoffwerk Dessau-Tornau GmbH (IDT), Oxford University/MRC	Phase I/I
Remune +/- AmpliVax	Whole-killed clade 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 clade B <i>nef</i> gene	FIT-Biotech	Phase I

replication during HAART interruptions, thereby reducing dependence on drug therapy over the long term. Although this is certainly a desirable outcome, there are as yet no convincing human data showing that it is achievable. Some researchers are optimistic about the prospects for this approach, while many others remain profoundly skeptical.

There is extensive overlap between the therapeutic and preventive vaccine fields, with many of

the same candidates being studied in both settings. ALVAC is a stalwart of therapeutic vaccine studies, despite its poor immunogenicity. A recent ANRS study found a statistically significant difference in post-treatment interruption control of viral load among recipients of a regimen that included ALVAC, lipopeptides, and IL-2 compared to participants receiving HAART alone. The numbers were small, however, and the average time to restarting HAART differed by only a matter of weeks (Levy 2005). Merck's Ad5 vaccine candidate is also being evaluated as a therapeutic in an ongoing ACTG study, although the construct being used encodes only the HIV *gag* gene and not the *pol* and *nef* genes that are included in the preventive trial.

Jonas Salk's Remune, amazingly, is edging its way towards two decades in human trials. Remune underwent a mild renaissance in the post-HAART era due to its one demonstrable talent, which is to induce HIV-specific CD4 T-cell responses capable of proliferating and producing IL-2 (Maino 2000). A tiny pilot study has hinted that these responses may also improve HIV-specific CD8 T-cell proliferation (Lichterfeld 2004), and trials using Remune in the context of treatment interruptions are continuing, although recent results from a study in acute HIV infection failed to show an effect of immunization on viral load (Perrin 2004). 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).

A new strategy for therapeutic immunization involves the use of dendritic cells (DCs). The job of DCs is to process and present small protein slices (called epitopes) of pathogens to T cells, thereby initiating an immune response (the job is known as antigen presentation). Several research groups are conducting trials wherein DCs are taken from an individual's blood and mixed with HIV proteins or epitopes, then reinjected to act as a vaccine. A small, uncontrolled pilot study recently claimed an immunologic and virological benefit to the approach in participants with early HIV infection who had yet to start HAART (Lu 2004), but these results await confirmation in larger controlled studies. It is unclear whether the approach can be rendered practical and cheap enough for widespread use.

Cytokines, Immunomodulators & Gene Therapy

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, with one recent ACTG study finding 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).

PRODUCT	ТҮРЕ	MANUFACTURER	STATUS
Interleukin-2 (IL-2)	Cytokine	Chiron	Phase III
HE2000	DHEA derivative	Hollis Eden	Phase II
Pegasys (peginterferon alfa-2a)	Cytokine	Roche Pharmaceuticals	Phase I b/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	Biotech Inflection Point	Phase I
IL-4/IL-13 trap	Anti-cytokines	Regeneron Pharmaceuticals	Phase I
Serostim	Human growth hormone	Serono	Phase not specified (ACTG 5174)
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	Intramural NIH Program, Roche Pharmaceuticals	Phase I

Table 5. Cytokines and Immunomodulators Pipeline

The mechanism of IL-2's effect is also uncertain, with recent evidence suggesting that over the long term it decreases T-cell proliferation and increases T-cell survival (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: SILCAAT and ESPRIT. IL-2's manufacturer, Chiron, originally sponsored SILCAAT, but in 2001 it pulled its support, and NIH (already the sponsor of the ESPRIT trial) had to step in to prevent the trial's termination. Preliminary results from the two trials should be available in 2005. An engineered and potentially less toxic form of IL-2 known as BAY 50-4798 is also under investigation in a phase I/II trial.

IL-7

IL-7 is a cytokine that 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. The ACTG has recently initiated a phase I trial in HIV infection.

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 the 2004 Retrovirus conference, 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 antigenpresenting 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 associated 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.

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

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. The unpegylated form of alpha interferon was studied for many years as a potential HIV therapy, but eventually abandoned due to under-whelming results. The newer pegylated form is now once again being studied as an adjunct to HAART and in the context of treatment interruptions.

HE2000

Another proposed enhancer of cell-mediated immune responses is the DHEA derivative HE2000, but no data have been published on this IBT, and many distrust the drug's developer, Hollis Eden, which has hyped the results from a small phase II South African study without ever managing to get them into the scientific literature. The company's web site currently states that they "are pursuing public/private partnerships to conduct a phase II/III clinical trial in infectious disease."

Immunosuppressive Agents

The association between heightened levels of immune activation and HIV disease progression has led some researchers to pursue studies of several drugs that are 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. Academic researchers nonetheless continue to evaluate their potential, typically as an adjunct to HAART or in the context of treatment interruptions. It seems unlikely that any of these agents will be approved for the treatment of HIV/AIDS, and there are no known novel drugs being evaluated (a lone cyclosporine derivative from Sandoz never made it to human trials).

CD4 Reinfusion

There is a grab bag of approaches involving infusing CD4 T cells that are isolated from HIVinfected individuals, expanded, in some cases genetically modified in the laboratory, and then reinfused as a potential IBT. NeoProbe's Activated Cellular Therapy (ACT) does not involve genetic modification, but expands CD4 T cells isolated from the lymph nodes using a technique designed to select the cells secreting HIV-suppressing factors such as beta-chemokines. Despite the publication of intriguing data from a pilot study of this approach (Triozzi 1999), the development of ACT is currently on hold pending identification of commercial partners that might support further research. 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, 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 (Deeks 2002; Amado 2002), but it remains very uncertain whether any of these gene therapy/IBT combinations will eventually enter efficacy trials.

Table 6. Gene Therapies Pipeline

PRODUCT	ТҮРЕ	MANUFACTURER	STATUS
CD4zeta modified CD4 and CD8 T cells	<i>Ex vivo</i> T cell Modifier	Cell Genesys	Phase II
Ribozymes (RRz2)	Antiviral ribozyme targeted against the <i>tat</i> gene, introduced into CD4 T cells via stem cells	Johnson & Johnson	Phase II
VRX496	Lentiviral vector encoding antiretroviral antisense, introduced into CD4 T cells <i>ex vivo</i>	VIRxSYS	Phase I
HGTV43	Vector encoding antiretroviral antisense, introduced into CD4 T cells <i>ex vivo</i>	Enzo Biochem	Phase I
M87o	Entry inhibitor gene encoded by a lentiviral vector, introduced into CD4 T cells <i>ex vivo</i>	EUFETS AG	Phasel

Online Resources

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

Global Campaign for Microbicides Pipeline Fact Sheet http://www.global-campaign.org/clientfiles/FS3-Pipeline-May05.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/

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

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

TAG Immune-Based Therapy Pipeline Chart http://www.aidsinfonyc.org/tag/science/IBTpipeline.html

References

Allen TM, Mortara L, Mothe BR, et al. Tat-vaccinated macaques do not control simian immunodeficiency virus SIVmac239 replication. J Virol 76(8):4108-12, 2002

Amado R, Mitsuyasu R, Rosenblatt J, et al. Development of genetically protected T-lymphocytes from transduced hematopoietic progenitors in human immunodeficiency virus-1 infected patients. Abstract # LbOr10, XIV International AIDS Conference, Barcelona, Spain, July 7-12 2002

Angel JB, High K, Rhame F, et al. Phase III study of granulocyte-macrophage colony-stimulating factor in advanced HIV disease: effect on infections, CD4 cell counts and HIV suppression. AIDS 14;4:387-395, 2000

Boritz E, Palmer BE, Wilson CC. Human immunodeficiency virus type 1 (HIV-1)-specific CD4+ T cells that proliferate in vitro detected in samples from most viremic subjects and inversely associated with plasma HIV-1 levels. J Virol 78;22:12638-46, 2004

Burton DR, Desrosiers RC, Doms RW, et al. Public health: A sound rationale needed for phase III HIV-1 vaccine trials. Science 303;5656:316, 2004

Cafaro A, Caputo A, Fracasso C, et al. Control of SHIV-89.6P-infection of cynomolgus monkeys by HIV-1 Tat protein vaccine. Nat Med 5;6:643-50, 1999

Carcelain G, Debre P, Autran B. Reconstitution of CD4+ T lymphocytes in HIV-infected individuals following antiretroviral therapy. Curr Opin Immunol 13(4):483-8, 2001

Coplan PM, Gupta SB, Dubey SA, et al. Cross-reactivity of anti-HIV-1 T cell immune responses among the major HIV-1 clades in HIV-1-positive individuals from 4 continents. J Infect Dis 191;9:1427-34, 2005

Davis NL, Caley IJ, Brown KW, et al. Vaccination of macaques against pathogenic simian immunodeficiency virus with Venezuelan equine encephalitis virus replicon particles. J Virol 74;1:371-8, . 2000

Deeks SG, Wagner B, Anton PA, et al. A phase II randomized study of HIV-specific T-cell gene therapy in subjects with undetectable plasma viremia on combination antiretroviral therapy. Mol Ther 5;6:788-97, 2002

De Paoli P. Immunological effects of interleukin-2 therapy in human immunodeficiency virus-positive subjects. Clin Diagn Lab Immunol. 8;4:671-7, 2001

Follmann D, Gilbert P, Self S, et al. An Independent Analysis of the Effect of Race in VAX004. Abstract #106, 11th Conference on Retroviruses and Opportunistic Infections, San Francisco CA, February 8-11, 2004

Fry TJ, Mackall CL. The Many Faces of IL-7: From Lymphopoiesis to Peripheral T Cell Maintenance. J Immunol 174(11):6571-6, 2005

Fry TJ, Moniuszko M, Creekmore S, et al. IL-7 therapy dramatically alters peripheral T-cell homeostasis in normal and SIV-infected nonhuman primates. Blood 101;6:2294-9, 2003

Flynn NM, Forthal DN, Harro CD, Judson FN, Mayer KH, Para MF; The rgp120 HIV Vaccine Study Group. Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. J Infect Dis 191;5:654-65, 2005

Gazzola L, Marchetti G, Bandera A, et al. Dynamics of T Cells Homeostasis Induced by Tucaresol. Abstract #523, 11th Conference on Retroviruses and Opportunistic Infections, San Francisco CA, February 8-11, 2004

Giri M, Ugen KE, Weiner DB. DNA vaccines against human immunodeficiency virus type 1 in the past decade. Clin Microbiol Rev 17;2:370-89, 2004

Guimaraes-Walker A, Mackie N, McMichael A, et al. Priming with a candidate HIV-1 clade A DNA vaccine followed by booster with HIV-1 Clade A MVA vaccine in volunteers at low risk of HIV infection. Abstract #55, AIDS Vaccines 04, Lausanne, Switzerland, August 30-September 1, 2004

Harrer EG, Schmitt-Haendle M, Petzold B, et al. Phase-I-study with a MVA-BN-Nef vaccine in HIV-1 negative volunteers. Abstract# ThPeA7007, XV International AIDS Conference, Bangkok, Thailand, 2004

Horton H, Beckham C, Stucky J, et al. Induction of IL-2 secreting CD4+ T-cells capable of proliferation in seronegative subjects receiving the HIV-1 gp120/NefTat subunit vaccine. Abstract #54, AIDS Vaccines 04, Lausanne, Switzerland, August 30-September 1, 2004

Isaacs R. Impact of pre-existing immunity on the immunogenicity of adenovirus serotype 5-based vaccines. Abstract #69, AIDS Vaccines 04, Lausanne, Switzerland, August 30-September 1, 2004

Jaoko W, Omosa G, Bhatt K, et al. Safety and immunogenicity of DNA and MVA HIVA vaccines in phase I HIV-1 vaccine trials in Nairobi, Kenya. Abstract#56, AIDS Vaccines 04, Lausanne, Switzerland, August 30-September 1, 2004

Jefferys R, Harrington M. Outstanding questions on HIV vaccine trial. Science 305;5681:180, 2004

Kahn JO, Cherng DW, Mayer K, Murray H, Lagakos S. Evaluation of HIV-1 immunogen, an immunologic modifier, administered to patients infected with HIV having 300 to 549 x 10(6)/L CD4 cell counts: A randomized controlled trial. JAMA 284(17):2193-202, 2000

Kostense S, Koudstaal W, Sprangers M, et al. Adenovirus types 5 and 35 seroprevalence in AIDS risk groups supports type 35 as a vaccine vector. AIDS 18;8:1213-6, 2004

Krebs FC, Miller SR, Catalone BJ, et al. Sodium dodecyl sulfate and C31G as microbicidal alternatives to nonoxynol 9: Comparative sensitivity of primary human vaginal keratinocytes. Antimicrob Agents Chemother 44: 1954–1960, 2000

Leng Q, Bentwich Z, Magen E, et al. CTLA-4 upregulation during HIV infection: association with anergy and possible target for therapeutic intervention. AIDS 16;4:519-29, 2002

Levy Y, Gahery-Segard H, Durier C, et al. Immunological and virological efficacy of a therapeutic immunization combined with interleukin-2 in chronically HIV-1 infected patients. AIDS 19;3:279-86, 2005

Lichterfeld M, Kaufmann DE, Yu XG, et al. Loss of HIV-1-specific CD8+ T cell proliferation after acute HIV-1 infection and restoration by vaccine-induced HIV-1-specific CD4+ T cells. J Exp Med 200;6:701-12, 2004

Lu W, Arraes LC, Ferreira WT, Andrieu JM. Therapeutic dendritic-cell vaccine for chronic HIV-1 infection. Nat Med 10;12:1359-65, 2004

Maino VC, Suni MA, Wormsley SB, Carlo DJ, Wallace MR, Moss RB. Enhancement of HIV Type 1 Antigen-Specific CD4+ T Cell Memory in Subjects with Chronic HIV Type 1 Infection Receiving an HIV Type 1 Immunogen. AIDS Res Hum Retroviruses 16;18:2065-2066, 2000

Mayer KH, Peipert J, Fleming T, et al.Safety and tolerability of BufferGel, a novel vaginal microbicide, in women in the United States. Clin Infect Dis 32: 476–482, 2001

Migueles SA, Laborico AC, Shupert WL, et al. HIV-specific CD8+ T cell proliferation is coupled to perforin expression and is maintained in nonprogressors. Nat Immunol 3;11:1061-8, 2002

Moore JP, Shattock RJ. Preventing HIV-1 sexual transmission--not sexy enough science, or no benefit to the bottom line? J Antimicrob Chemother 52;6:890-2, 2003

Napolitano LA, Lo JC, Gotway MB, et al. Increased thymic mass and circulating naive CD4 T cells in HIV-1-infected adults treated with growth hormone. AIDS 16;8:1103-11, 2002

Nitayaphan S, Pitisuttithum P, Karnasuta C, et al. Safety and immunogenicity of an HIV subtype B and E prime-boost vaccine combination in HIV-negative Thai adults. J Infect Dis 190;4:702-6, 2004

Nugeyre MT, Monceaux V, Beq S, et al. IL-7 stimulates T cell renewal without increasing viral replication in simian immunodeficiency virus-infected macaques. J Immunol 171;8:4447-53, 2003

Pantaleo G, Koup RA. Correlates of immune protection in HIV-1 infection: what we know, what we don't know, what we should know. Nat Med 10;8:806-10, 2004

Parsey M, Fauci G, Dunn J, et al. Human Pharmacokinetic Evaluation of the IL-4/13 Trap: a Novel Immunomodulatory Agent for the Treatment of HIV Disease. Abstract #522, 11th Conference on Retroviruses and Opportunistic Infections, San Francisco CA, February 8-11, 2004

Perrin, L. Data on Quest Therapeutic Vaccination. Abstract # 31, AIDS Vaccines 04, Lausanne, Switzerland, August 30-September 1, 2004

Petrovas C, Mueller YM, Bojczuk P, et al. IL-15 Treatment of SIV-infected Non-human Primates. Abstract #512, 11th Conference on Retroviruses and Opportunistic Infections, San Francisco CA, February 8-11, 2004

Pitisutithum, P. Efficacy of AIDSVAX B/E Vaccines in Injecting Drug Use. Abstract #107, 11th Conference on Retroviruses and Opportunistic Infections, San Francisco CA, February 8-11, 2004

Russell ND, Graham BS, Keefer M, et al. A Phase II Double Blind Randomized Trial to Evaluate an HIV-1 Canarypox Vaccine (vCP1452) Alone and in Combination with Rgp120: Low Frequency T cell Responses. Abstract #408, Keystone Symposia on HIV Vaccines: Current Challenges and Future Prospects, Banff, Alberta, Canada, April 9-15, 2005

Salmon-Ceron D, Gahery H, Pialoux G, et al. Lipopeptides trials in non-HIV infected volunteers. Session V, XIIIth Cent Gardes Symposium on HIV and AIDS, Annecy, France, October 27-29, 2002

Schultz AM, Connell MM, Koff WC, Wyand M, Anklesaria P, Johnson, PR. Immunogenicity of two different AAV-based HIV vaccine candidates in non-human primates. Abstract# 16, AIDS Vaccines 04, Lausanne, Switzerland, August 30-September 1, 2004

Sereti I, Anthony KB, Martinez-Wilson H et al. IL-2-induced CD4+ T-cell expansion in HIV-infected patients is associated with long-term decreases in T-cell proliferation. Blood 104;3:775-80, 2004

Srivastava IK, VanDorsten K, Vojtech L, Barnett SW, Stamatatos L Changes in the immunogenic properties of soluble gp140 human immunodeficiency virus envelope constructs upon partial deletion of the second hypervariable region. J Virol 77(4):2310-20, 2003

Stafford MK, Ward H, Flanagan A, et al. Safety study of nonoxynol-9 as a vaginal microbicide: Evidence of adverse effects. J Acquir Immune Defic Syndr Hum Retrovirol 17: 327–331, 1998

Stratov I, Dale CJ, Chea S, McCluskey J, Kent SJ. Induction of T-cell immunity to antiretroviral drug-resistant human immunodeficiency virus type 1. J Virol 79;12:7728-37, 2005

Sumida SM, Truitt DM, Lemckert AA, et al. Neutralizing Antibodies to Adenovirus Serotype 5 Vaccine Vectors Are Directed Primarily against the Adenovirus Hexon Protein. J Immunol 174;11:7179-85, 2005

Triozzi PL, Aldrich W, Bresler HS, et al. Cellular immunotherapy of advanced human immunodeficiency virus type 1 infection using autologous lymph node lymphocytes: effects on chemokine production. J Infect Dis 179;1:245-8, 1999

Valdez H, Mitsuyasu R, Landay A, et al. Interleukin-2 Increases CD4+ lymphocyte numbers but does not enhance responses to immunization: results of A5046s. J Infect Dis 187(2):320-5, 2003

Van Damme L, Ramjee G, Alary M, et al. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: A randomised controlled trial. Lancet 360: 971–977, 2002

Waldmann TA, Dubois S, Tagaya Y. Contrasting roles of IL-2 and IL-15 in the life and death of lymphocytes: implications for immunotherapy. Immunity 14(2):105-10, 2001

Weber J, Nunn A, O'Connor T, Jeffries D, et al. 'Chemical condoms' for the prevention of HIV infection: evaluation of novel agents against SHIV(89.6PD) *in vitro* and *in vivo*. AIDS 15(12):1563-8, 2001

Woolfson AD, Malcolm RK, Gallagher R. Drug delivery by the intravaginal route. Crit Rev Ther Drug Carrier Syst 17;5:509-55, 2000

The Hepatitis C Virus (HCV) Treatment Pipeline

by Tracy Swan with special thanks to Daniel Raymond

HCV and HIV/HCV Prevalence

Almost 129 million people—an estimated 2% of the world's population—have been infected with the hepatitis C virus (HCV) (Global Burden of Hepatitis C Working Group 2004; United States Census Bureau 2005). Approximately 20% (nearly 26 million people) may be expected to develop cirrhosis over a 20- to 50-year period (Alberti 1999; Dore 2002; Freeman 2001; Freeman 2003; Poynard 1997; Poynard 2001). These statistics indicate the immense need for effective, non-toxic, and affordable treatments for hepatitis C.

In the United States, at least 3.8 million people have been infected with HCV and most have developed chronic infections (Armstrong 2004). HCV-related end-stage liver disease is the leading reason for liver transplantation (CDC 1998). HCV-related mortality increased by 220% from 1993 to 1998 (Vong 2004), and morbidity and mortality from hepatitis C are projected to rise sharply in the next fifteen years as a reflection of the large numbers of hepatitis C infections that occurred during the 1980s (Davis 2003). As many as 10,000 to 12,000 deaths each year are now attributed to complications of hepatitis C (CDC 1998; NIH 2002).

Hepatitis C is also an opportunistic infection of HIV disease. Graham and colleagues reported that HIV coinfection significantly increases the risk of developing serious liver disease, doubles the risk of cirrhosis, and increases the risk of decompensated liver disease by more than six times (Graham 2001). In the HAART era, end-stage liver disease from hepatitis C coinfection has emerged as a leading cause of death among HIV-positive people (Bica 2001; Martin-Carbonero 2001; Rosenthal 2003).

At least 25% of all HIV-positive persons in the United States are HCV-coinfected (Sulkowski 2003; Thomas 2002). In the EuroSIDA cohort, overall HCV prevalence is reported at 34%, with the highest prevalence found in Eastern and Southern Europe (47.7% and 44.9%, respectively) (Rockstroh 2004).

HCV Treatment: The Current Landscape

The standard of care therapy for treating hepatitis C virus (HCV) is 24 to 48 weeks with a onceweekly injection of pegylated interferon plus daily ribavirin capsules, tablets, or liquid. Although pegylated interferon is more effective than its predecessor, standard interferon, HCV treatment is far from optimal; substantial limitations to efficacy and tolerability remain. Overall, approximately 50% of treatment-naïve people will achieve a sustained virological response (SVR; meaning that there is no detectable hepatitis C virus in the bloodstream six months after completion of therapy). Attaining SVR usually indicates that a person will remain virus-free for years; many consider it a cure.

When response rates are examined more closely, however, a grimmer scenario emerges. SVR rates are significantly lower among certain groups, particularly those who have the greatest need for treatment: people with HCV genotype 1 and a high viral load (who constitute the majority of HCV cases in the United States); African Americans, (the population with the highest-prevalence in the US); individuals with advanced liver damage; HIV/HCV-coinfected persons; previously treated non-responders and relapsers; and liver transplant recipients, virtually all of whom develop recurrent HCV infection.

STUDY	REGIMEN*	POPULATION	% SVR
Manns 2001	PEG-IFN alfa-2b + RBV for 48 weeks	Genotype 1, high viral load (>2,000,000 copies)	30% (78/256)
Muir 2004	PEG-IFN alfa-2b + RBV for 48 weeks	African Americans and non-Hispanic Whites, all genotype 1	For African Americans: 19% (19/100) For non-Hispanic Whites: 52% (52/100)
Fried 2002	PEG-IFN alfa-2a + RBV for 48 weeks	Cirrhotics	43% (24/56)
Torriani 2004	PEG-IFN alfa-2a + RBV for 48 weeks	HIV/HCV-coinfected, with genotype 1	29% (51/176) Low viral load: 61% (28/46) High viral load: 18% (23/130)
Shiffman 2004	PEG-IFN alfa-2a + RBV for 48 weeks	Non-responders to previous IFN therapy who have bridging fibrosis or cirrhosis	18% (109 /604)
Dumortier 2004	PEG-IFN alfa-2b + RBV for 48 weeks	Liver transplant recipients with recurrent HCV	45% (9/20)

Table 1. Sustained Virological Response Rates by Baseline Characteristics: Data From Five Trials

* Dosing of PEG-IFN and RBV differs across studies.

Side effects from HCV treatment are daunting, although management strategies continue to evolve. People may suffer from a constellation of adverse events, including fatigue; neuropsychiatric side effects (depression ranging from mild to suicidal, and suicide in <1 to 2% of study participants, irritability, anxiety, and insomnia); hematological toxicities (anemia, neutropenia, and thrombo-cytopenia) and flulike symptoms (Russo 2003). Poor tolerability of treatment often results in discontinuation of therapy (Aspinall 2004) or dose reduction, which may compromise efficacy (Ong 2004).

Hepatitis C treatment is less effective for coinfected persons than for those with HCV monoinfection (Carrat 2004; Chung 2004; Fried 2002; Hadziyannis 2004; Manns 2001; Torriani 2004). Tolerating HCV treatment is often more difficult for HIV/HCV-coinfected persons and mono- and coinfected liver transplant recipients. Side effects are often more severe and adverse events more frequent, as reflected in the high discontinuation rates in HCV treatment trials involving coinfected persons (Cargnel 2005; Carrat 2004). Concomitant HIV therapy must be selected carefully to avoid interactions with ribavirin; in particular, the interaction between ribavirin and didanosine (ddI; Videx®) can be life-threatening (Bristol Myers Squibb 2004; Fleischer 2003).

Until new therapies become available, research on optimizing efficacy and tolerability of the current HCV treatment regimen must continue in tandem with operational research on delivery of HCV treatment, since it is likely that interferon will continue to be the backbone of future treatment regimens. Strategies for managing interferon-induced depression, which is also a common co-morbidity of hepatitis C and HIV, must be rigorously explored. Models of care for active drug users, among whom HCV is highly prevalent, must be developed and evaluated.

Maintenance therapy with pegylated interferon may provide non-responders, relapsers, and cirrhotics with a bridge until better treatments are available. Much remains to be learned about managing interactions among immunosuppressants, antiretroviral therapies, and HCV treatment in coinfected transplant recipients.

Desired Elements of Future Therapies

Given the drawbacks of current HCV treatment, there is ample room for improvements in the safety, efficacy, and tolerability of HCV therapy. Ideally, new treatments will replace pegylated interferon and ribavirin; at the least, they should augment the current standard of care. Improvements in future therapy options may include:

- Increased efficacy, which is particularly important for all HIV/HCV-coinfected persons, as well as persons with HCV genotype 1 and high viral load, African Americans, persons with advanced liver damage, relapsers and non-responders, and transplant recipients with recurrent HCV.
- Less toxicity.
- Anti-inflammatory and antifibrotic therapies to reverse, or at least to stabilize, progression of liver disease.

In addition,

- Second-line therapies are needed for an increasing population of non-responders to pegylated interferon and ribavirin.
- New drugs will need to be potent and have a high genetic barrier, to prevent development of resistance.
- Non-injectable therapies are needed, since some former drug users are not comfortable with injection, due to concerns about relapse to active drug use. This is especially vital given the side effects of interferon, which mimic opiate withdrawal symptoms. An additional benefit of oral therapies would be the elimination of injection site reactions.
- New drugs must be affordable, so that treatment is accessible to all individuals who require it.

The HCV Pipeline

A combination of drugs will be necessary to treat HCV since, as with HIV, resistance to a single agent is likely to develop eventually. Currently, the most promising areas of HCV drug development involve oral drugs that inhibit hepatitis C's protease and polymerase enzymes—a strategy that has proven successful as part of suppressive, multidrug therapy for HIV.

Many new anti-HCV agents and other therapeutics are in preclinical development. Some of the mechanisms involve RNA interference, internal ribosomal entry-site inhibition, and dual monoclonal antibodies to prevent recurrence of HCV after liver transplantation. A few companies have candidates entering phase I in the near future. Gilead Sciences, Inc., and Achillion, who share a research and end-licensure agreement for ACH-806, their HCV protease inhibitor, are planning a phase I study for the end of 2005. Nevertheless, interferon will likely continue to be the backbone of most foreseeable regimens. Different types and formulations of interferon that may mitigate its toxicity are currently in development (as is a more tolerable version of ribavirin). Research on therapies that modulate the immune response to hepatitis C is ongoing as well, though these drugs may not ultimately be as effective for HIV-positive persons and transplant recipients on immunosuppressive drugs.

Hepatitis C Pro	Hepatitis C Protease Inhibitors (oral)		
<i>Vertex</i> VX-950	Phase Ib Completed	Demonstrated potent antiviral activity against HCV genotype 1 at all doses, especially at 750 mg every eight hours. In healthy volunteers, adverse events (headache, nausea, diarrhea, frequent urination, and sleepiness) were mild. Safety data from study volunteers with HCV are being analyzed. VX-950 will be used in combination with other drugs, as resistance is likely to develop.	
<i>Schering-Plough</i> Not named	Phase I	Virtually no information available.	

Hepatitis C Polymerase Inhibitors (oral)

Г

<i>l denix</i> Valopicitabine (NM283)	Phase II a	Studied in HCV genotype 1; greatest reduction in HCV RNA (0.41 to 2.37 log ₁₀) with 800 mg/day. No serious adverse events or consistent laboratory abnormalities were reported; most common (mild and limited) side effects were nausea and occasional vomiting; currently being evaluated in combination with pegylated interferon alfa-2b. The phase II a study has been extended to 48 weeks; so far, data to week 24 are available.
<i>Japan T obacco</i> JTK-003	Phase II	Currently being studied in Japan and the U.S.; no additional information is available.
<i>ViroPharma & Wyeth</i> HCV-796	Phase Ib	A randomized, double-blind, placebo-controlled study comparing multiple ascending doses of HCV-796 in 96 treatment-naïve study volunteers was announced in May, 2005; data from this study are expected in the fourth quarter of 2005.

Hepatitis CIMPDH (inosine monophosphate) Inhibitors (oral)

<i>Vertex</i> Merimepodib (VX-497)	Phase IIb	Currently being studied in non-responders in combination with pegylated interferon alfa-2a plus ribavirin.
--	-----------	--

Potential Replacement for Ribavirin (oral)

<i>Valeant</i> Viramidine	Phase III	Viramidine is a prodrug of ribavirin. It does not appear to be more effective than ribavirin; viramidine's major advantage is tolerability; in phase II, the incidence of anemia was significantly lower with viramidine than ribavirin, regardless of viramidine dose. Currently, two international, multicenter phase III trials are evaluating 600 mg/BID of viramidine in combination with pegylated interferon alfa-2a (VISER-1) or pegylated interferon alfa-2b (VISER-2).
------------------------------	-----------	--

Table 2. What's in Clinical Development: The Pipeline Chart (Cont.)

Hepatitis C Cas	Hepatitis C Caspase Inhibitors (oral)			
<i>Pfizer/l du n pharmaceu ticals</i> IDN-6556	Phase II	Apoptosis (programmed cell death) inhibitor. Although no decreases in HCV RNA >0.5 were reported after 14 days, significant decreases in ALT and AST levels occurred at all doses. Adverse events were mild (dry mouth, headache, and stomach ache). FDA has granted orphan drug status for IDN-6556 when used after organ transplantation.		
New Types and	Formulation	ons of Interferon (injection; subcutaneous infusion/implant)		
Intarcia Therapeutics Omega Interferon DUROS® implant	Phase II	A 48-week course of daily subcutaneous infusions of omega interferon, with or without ribavirin, is being evaluated in treatment-naïve people with hepatitis C, genotype 1; the study is located in Moscow and St. Petersburg. Intarcia has acquired the rights to a subcutaneous implant that continuously delivered omega interferon for up to three months in animal studies; clinical testing will be initiated in 2005.		
<i>Human Genome Sciences</i> Albuferon	Phase II b	A long-acting formulation of interferon-alfa made by fusing it with albumin. A phase II study evaluated five doses (200, 450, 670, 900, or 1,200 micrograms [mcg]) given 14 days apart by subcutaneous infusion to 56 treatment-naïve people. Twenty-eight days after the second infusion, 23% of participants in the 900 and 1,200 mcg groups had undetectable HCV RNA. Albuferon's mean half-life was 148 hours, supporting two-to-four week dosing. Mild-to-moderate adverse advents were reported, with only one severe adverse event (colitis), which resolved after albuferon was discontinued. An open-label, controlled, four-arm phase IIb study is evaluating safety and efficacy of three doses of albuferon plus ribavirin in treatment-naïve individuals with HCV genotype 1; the control arm will receive pegylated interferon alfa-2a plus ribavirin. An ongoing randomized, open-label dose-escalation study in non-responders is evaluating safety and efficacy of 48 weeks of three to four different doses of albuferon with weight based-ribavirin.		
Antivirals (oral)				
<i>Migenix</i> Celgosivir (MBI-3253)	Phase II a	An inhibitor of alpha-glucosidase. A 12-week safety, activity, and dosing study. Celgosivir is being evaluated in 60 study volunteers with HCV genotype 1 who are treatment-naïve or interferon-intolerant.		
Therapeutic Va	ccines			
/ <i>ntercell</i> IC41	Phase II	Designed to induce T-cell responses to HCV. Evaluated in non-responders; HCV-specific CD4 and CD8 T-cell responses were induced in 58% (36/60); a subset (6/29) had a transient virological response. An ongoing phase II study is evaluating response to IC41 in 50 healthy volunteers using different dosing schedules.		
/ <i>nnogenetics</i> INN0101	Phase I <i>I</i> Ib	Uses HCV genotype 1b envelope protein (E1) to elicit immune response. Phase I/II: safety, efficacy, and tolerability of INNO101 expressed in yeast in 122 volunteers with hepatitis C; results expected at the end of 2005. A phase IIb evaluation of the effect of INNO101 vs. placebo on liver fibrosis and inflammation among 164 volunteers with HCV genotype 1 has yielded inconclusive results and may be extended for an additional 15 months, pending approval by the investigators.		
Monoclonal An	tibodies (in	ifusion)		
<i>Peregrine</i> Tarvicin™	Phase I	Tarvicin [™] targets the envelope of HCV and the membrane of HCV-infected cells. A dose-escalation study in 32 non-responders to previous HCV therapy is evaluating safety, pharmacokinetics, and hepatitis C viral load after a single infusion of Tarvicin [™] .		

Table 2. What	's in (Clinical	Development:	The	Pipeline	Chart	(Cont.)
---------------	---------	----------	---------------------	-----	----------	-------	---------

Immunomodulators (injection, oral)					
Anadys ANA971 (oral) Anadys/Novartis ANA975 (oral)	Phase I	971 and 975 are oral prodrugs of ANA245 (Isatoribine), a nucleoside analog that stimulates immune responses. Safety, pharmacokinetics, and immune responses to ANA971 are being evaluated in 30 healthy volunteers. ANA975 is expected to enter phase I in the second half of 2005.			
<i>Coley</i> Actilon™ (CPG 10101)	Phase Ib Completed	A synthetic agonist of the Toll-like receptor 9 (TLR-9); Actilon [™] stimulates immune responses and production of endogenous type 1 interferon. A phase Ib, double-blind, dose-ranging study of Actilon [™] in genotype 1 non-responders and healthy volunteers reported dose-dependent decreases in HCV RNA. The highest dose evaluated was 20 micrograms, given twice weekly, for four weeks. Transient hematological changes, mild-to-moderate injection site reactions, and flulike symptoms were reported.			
SciClone Pharmaceuticals Zadaxin® (thymosin alpha 1; thymalfasin)	Phase III in U.S. & Europe	Synthesized human thymus gland extract. The U.S. phase II study compared six months of interferon monotherapy to Zadaxin® + interferon, vs. placebo. Non-responders were offered six additional months of combination therapy. The primary endpoint of this study was sustained biochemical response (normal ALT levels for six months after completion of therapy). Although people treated with combination therapy had a higher rate of sustained biochemical response, it is difficult to evaluate these data, as some participants were treated for six months and others for twelve. Two U.S. phase III studies are comparing Zadaxin® plus pegylated interferon to pegylated interferon monotherapy in non-responders; results are expected in early 2006. A European phase III trial evaluating Zadaxin® in combination with pegylated interferon and ribavirin is underway. Zadaxin® is also being evaluated for treatment of lung and liver cancer, as a vaccine adjuvant, and as an HIV therapy in combination with interferon and AZT. European studies are being conducted by SciClone's partner, Sigma-Tau.			

Off-Label Use and Pilot Studies

Interferon-gamma 1-b (Actimune[®]) has been approved for treatment of chronic granulomatous disease and severe, malignant osteopetrosis. There are several ongoing pilot studies in nonresponders that combine Actimune® with interferon alfacon-1, ribavirin, and pegylated interferon.

Intermune's interferon-alfacon-1 (Infergen®), a synthetic consensus sequence of interferon-alfa subtypes, is approved for HCV treatment in persons with compensated liver disease; it is currently being evaluated with ribavirin in a phase III study of non-responders.

Impact of New Drugs on Current Research & Treatment Paradigms

Given what we know about hepatitis C viral kinetics and the relationship between early virological response to treatment and treatment outcome, it is reasonable to develop innovative methods of evaluating the efficacy of these new drugs. An effective and potent combination of oral antiviral drugs could potentially be used as a lead-in for pegylated interferon, hopefully increasing efficacy by rapidly driving down HCV RNA and shortening duration of therapy. Since, as with anti-HIV drugs, the threat of drug resistance is a concern, it will be crucial to determine how quickly HCV drug resistance develops with each new agent and to tailor clinical trials and treatment paradigms accordingly.

Given the increasing mortality rates among HIV/HCV-coinfected persons from end-stage liver disease, and given the accelerated progression of hepatitis C in HIV/HCV-coinfected people, it is crucial that the efficacy and safety of new HCV therapies and potential interactions with antiretroviral agents be evaluated in coinfected persons. Important goals for the HCV and HIV/HCV advocacy communities are:

- **a.** Including HIV/HCV-coinfected persons as soon as safety and activity have been demonstrated in HCV-monoinfected study volunteers;
- **b.** Enrolling sufficient numbers of African-American mono- and coinfected persons, so that safety and efficacy of novel HCV therapies can be evaluated in African Americans;
- **c.** Developing "real-life" studies and inclusion criteria to ensure that results from clinical trials are relevant to high-prevalence populations: active drug and alcohol users; persons on methadone, buprenorphine, or heroin substitution therapy; and people with psychiatric disorders; and
- **d.** Performing trials in hard-to-treat populations, i.e., people with genotype 1 and high hepatitis C viral loads, cirrhotics, non-responders, relapsers, and transplant recipients.

Companies experienced in working with the HIV/AIDS community have been more receptive to community input than those with no history of community collaboration. Relationships must be built and cultivated with inexperienced companies so that they recognize the value of input from the HCV and HIV communities.

Timeline for New Therapies

While it certainly is reasonable to offer patients the anticipation of future treatment opportunities, hope is not a particularly effective method of viral eradication.

—Kenneth E. Sherman, Stephen D. Zucker Gastroenterology 2004

The HCV treatment pipeline is robust, but it will probably be at least five years until many new therapies become widely available. Several promising compounds have already fallen by the wayside during clinical development. A case in point is BILN-2061, Boehringer Ingelheim's HCV protease inhibitor, which offered exciting proof-of-concept data (Lamarre 2003) but was shelved due to animal toxicity. People living with hepatitis C and HIV/HCV coinfection and their clinicians are eagerly awaiting new therapies. Decisions to defer HCV treatment until better therapies are available must be informed by accurate, up-to-date information on the status of new therapies. This information should be easily accessible and available to all stakeholders.

References

Alberti A, Chemello L, Benvegnu L. Natural history of hepatitis C. J Hepatol. 1999;31 Suppl 1:17-24.

Armstrong GL, Simard EP, Wasley A, McQuillan GM, Kuhnert WL, Alter MJ. (Abstract 31). The prevalence of hepatitis C virus (HCV) infection in the United States, 1999-2002. 55th Annual Meeting of the American Association for the Study of Liver Disease. Boston, Massachusetts. 2004.

Aspinall RJ, Pockros PJ. The management of side-effects during therapy for hepatitis C. Aliment Pharmacol Ther. 2004 Nov 1;20(9):917-29.

Bica I, McGovern B, Dhar R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. Clin Infect Dis. 2001 Feb 1;32(3):492-7.

Bristol Myers Squibb. Videx® prescribing information. 2004.

Cargnel A, Angeli E, Mainini A, et al; Italian Co-infection Study (ICOS) Group. Open, randomized, multicentre italian trial on PEG-IFN plus ribavirin versus PEG-IFN monotherapy for chronic hepatitis C in HIV-coinfected patients on HAART. Antivir Ther. 2005;10(2):309-17.

Carrat F, Bani-Sadr F, Pol S, et al; ANRS HCO2 RIBAVIC Study Team. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. JAMA. 2004 Dec 15;292(23):2839-48.

Centers for Disease Control. Morbidity and Mortality Weekly Report. Recommendations for Prevention and Control of Hepatitis C Virus (HCV Infection and HCV-Related Chronic Disease. October 16th,1998/47(RR19); 1-39).

Chung RT, Andersen J, Volberding P, et al; AIDS Clinical Trials Group A5071 Study Team. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. N Engl J Med. 2004 Jul 29;351(5):451-9.

Davis GL, Albright JE, Cook SF, Rosenberg DM. Projecting future complications of chronic hepatitis C in the United States. Liver Transpl. 2003 Apr;9(4):331-8.

Dore GJ, Freeman AJ, Law M, Kaldor JM. Is severe liver disease a common outcome for people with chronic hepatitis C? Gastroenterol Hepatol. 2002 Apr;17(4):423-30.

Dumortier J, Scoazec JY, Chevallier P, Boillot O. Treatment of recurrent hepatitis C after liver transplantation: a pilot study of peginterferon alfa-2b and ribavirin combination. J Hepatol. 2004 Apr;40(4):669-74.

Fleischer R, Boxwell D, Sherman KE. (abstract 763). Evidence suggesting mitochondrial toxicity in HIV/HCV coinfected patients receiving ribavirin and didanosine. 10th Conference on Retroviruses and Opportunistic Infections. Boston, Massachusetts. 2003.

Freeman AJ, Dore GJ, Law MG, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. Hepatology. 2001 Oct;34(4 Pt 1):809-16.

Freeman AJ, Law MG, Kaldor JM, Dore GJ. Predicting progression to cirrhosis in chronic hepatitis C virus infection. J Viral Hepat. 2003 Jul;10(4):285-93.

Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002 Sep 26;347(13):975-82.

Global Burden Of Hepatitis C Working Group. Global burden of disease (GBD) for hepatitis C. J Clin Pharmacol. 2004 Jan;44(1):20-9.

Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis. 2001 Aug 15;33(4):562-9

Hadziyannis SJ, Sette H Jr, Morgan TR, et al;PEGASYS International Study Group. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med. 2004 Mar 2;140(5):346-55.

Lamarre D, Anderson PC, Bailey M, et al. An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus. Nature. 2003 Nov 13;426(6963):186-9

Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001 Sep 22;358(9286):958-65.

Martin-Carbonero L, Soriano V, Valencia E, Garcia-Samaniego J, Lopez M, Gonzalez-Lahoz J. Increasing impact of chronic viral hepatitis on hospital admissions and mortality among HIV-infected patients. AIDS Res Hum Retroviruses. 2001 Nov 1;17(16):1467-71.

Muir AJ, Bornstein JD, Killenberg PG; Atlantic Coast Hepatitis Treatment Group. Peginterferon alfa-2b and ribavirin for the treatment of chronic hepatitis C in blacks and non-Hispanic whites. N Engl J Med. 2004 May 27;350(22):2265-71

National Institutes of Health Consensus Development Conference Statement. Management of Hepatitis C: 2002. http://consensus.nih.gov/cons/116/091202116cdc statement.htm (accessed on April 30th, 2005).

Ong JP, Younossi ZM. Managing the hematologic side effects of antiviral therapy for chronic hepatitis C: anemia, neutropenia, and thrombocytopenia. Cleve Clin J Med. 2004 May;71 Suppl 3:S17-21.

Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet. 1997 Mar 22;349(9055):825-32.

Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J.

Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis c. J Hepatol. 2001 May;34(5):730-9.

Rockstroh J, Konopnicki D, Soriano V, et al; EuroSIDA study group. (abstract 799) Hepatitis B and Hepatitis C in the EuroSIDA Cohort: Prevalence and Effect on Mortality, AIDS Progression and Response to HAART. 11th Conference on Retroviruses and Opportunistic Infections. San Francisco, California. 2004.

Rosenthal E, Poiree M, Pradier C, et al; GERMIVIC Joint Study Group. Mortality due to hepatitis C-related liver disease in HIV-infected patients in France (Mortavic 2001 study). AIDS. 2003 Aug 15;17(12):1803-9.

Russo MW, Fried MW. Side effects of therapy for chronic hepatitis C. Gastroenterology. 2003 May;124(6):1711-9.

Shiffman ML, Di Bisceglie AM, Lindsay KL, et al; Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis Trial Group. Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. Gastroenterology. 2004 Apr;126(4):1015-23.

Sulkowski MS, Thomas DL. Hepatitis C in the HIV-Infected Person. Ann Intern Med. 2003 Feb 4;138(3):197-207.

Thomas DL. Hepatitis C and human immunodeficiency virus infection. Hepatology. 2002 Nov;36(5 Suppl 1):S201-9.

Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al; APRICOT Study Group. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med. 2004 Jul 29;351(5):438-50.

United States Census Bureau. World population clock. http://www.census.gov/ipc/www/world.html (accessed on 28th May 2005).

Vong S, Bell BP. Chronic Liver Disease Mortality in the United Stares, 1990-1998. Hepatology. 2004 Feb 39;(2):476-83.

Zucker SD, Sherman KE. Beyond interferon for Hepatitis C: living in the present while hoping for the future. Gastroenterology. 2004 May;126(5):1487-8.

The Tuberculosis (TB) Treatment Pipeline by Javid Syed

Although tuberculosis (TB) kills two million people a year—one person every 15 seconds—there have been no new drugs approved to treat TB in the last 40 years. According to the World Health Organization (WHO), the global incidence of TB disease is rising by 1% annually. This increase is concentrated in Africa and is attributable to the rise in TB infection in people with HIV. Additionally, the emergence of multidrug-resistant TB (MDR-TB) in Eastern Europe and Russia is posing a new challenge to efforts to control the disease.

TB is a disease of the poor. Ninety-five percent of those ill with TB, and 98% of those who die of TB, live in the developing world. Despite significant investment on the part of the affected countries, there is still a great need for multilateral resources and political commitment to adequately address the health-infrastructure and financing challenges of which the TB epidemic is both a product and a cause. The Global Plan to Stop TB (2001–2005) identified a resource gap of \$3.77 billion, which did not fully encompass the need for investment in new tools (including diagnostics, drugs, and vaccines), and which in any case was not fully funded (Global Partnership to Stop TB 2001).

Beyond the epidemiological and political context, there are also significant biomedical issues that new treatments need to help alleviate. Some of these concerns are:

- Length of treatment. Initial first-line therapy for uncomplicated sputum smear-positive pulmonary TB takes 6–8 months. This treatment consists of four medications taken at least three times a week for two months and followed by 4–6 months of two medications daily. The recommended first-line regimen consists of isoniazid (H), rifampin (R), pyrazinamide (Z), and ethambutol (E) (HRZE) for two months daily or thrice weekly, followed by four months of HR or six months of HE. HR is preferred since it produces fewer relapses, especially among HIV-infected persons, but due to drug interactions with many antiretroviral drugs (ARVs), its implementation remains problematic in many places (Jindani 2004; Harries 2004a).
- Drug interactions with ARVs. Rifampin, a crucial drug in first-line regimens, reduces the concentration of most ARVs, precluding its use with the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine or most protease inhibitors (PIs). This severely limits the ability of people coinfected with HIV and TB, who need therapy for both conditions, to access treatment. Thus there need to be more TB drugs available that are as effective as rifampin, but that can be taken with more ARV regimens (Harries 2004b).
- Adverse events. Though TB drugs are generally well tolerated, they can have significant adverse effects and in some cases are contraindicated. Some of the more common adverse events/contraindications with first-line TB drugs include (Harries 2004b):

Drug	Adverse Event/Contraindication
Isoniazid	Peripheral neuropathy
Pyrazinamide	Hepatitis
Rifampin	Hepatitis, GI reactions
Streptomycin	Contraindicated during pregnancy
Thiacetazone	Severe skin rash among HIV+ (not recommended)

- Need for drugs effective against MDR-TB. MDR-TB is any strain of TB that is resistant to the bactericidal effects of rifampin (R) and isoniazid (H). According to Médecins Sans Frontières (Doctors without Borders), approximately 250,000–400,000 new cases of MDR-TB each year globally are added to 500,000 or more ongoing cases (MSF 2005). In parts of the Baltic States, Russian Federation, Ukraine, and Central Asia, TB patients are ten times more likely to have MDR-TB. In the Tomsk Oblast of Russia, MDR cases have risen to nearly 14% of TB cases (WHO 2004). A significant proportion of the TB cases in this region are among injecting drug users (IDUs) who are also at significant risk for HCV and HIV coinfections; there is, therefore, an urgent need for a new TB treatment that has low liver toxicity.
- Pediatric TB. In 2004, the global burden of pediatric TB was estimated to be ten percent of total TB cases. This accounted for 1.5 million new cases and 130,000 deaths. Pediatric TB is often smear-negative (even among HIV-negative children), and it is therefore often under diagnosed, and untreated. There is an urgent need to improve pediatric access to TB treatment and to develop TB drugs, including fixed-dose combinations (FDCs), which are safe and effective among children (Chauhan 2004).

To address these urgent, emerging challenges for TB control, there has been recent unprecedented activity in the arena of TB drug development. Agencies such as WHO, the Global Fund for HIV, TB, and Malaria, and the Gates Foundation have galvanized multilateral support and initiated public-private partnerships to increase resources to combat this disease of poverty. One result of these actions is that after a lull of 40 years, six new drugs for TB are currently in clinical trials. At least three other potentially exciting compounds are in preclinical studies. These compounds are products of research and development undertaken by pharmaceutical companies and public-private collaborations funded through philanthropic foundations. One leader championing the cause of TB drug development is the nonprofit Global Alliance for TB Drug Development, which is supported by the Gates and Rockefeller Foundations. The Global Alliance has catalyzed a new focus and leadership for TB treatments by initiating public-private partnerships among stakeholders doing basic science and clinical trials.

The Draft Strategic Plan of the New Drugs Working Group for the Global Plan to Stop TB-II includes the following drugs that are currently or imminently scheduled for clinical trials (New Drugs Working Group Draft for Global Plan II April 2005). All the compounds in this unprecedented TB drug pipeline have been endorsed by the Global Alliance and are being screened to ensure that they can be taken with ARVs, manufactured inexpensively for use in developing countries, and used with other TB drug regimens, ideally to shorten and simplify the duration of TB treatment and address MDR-TB (New Drugs Working Group 2005).

Drug Name(s)	Drug Class	Sponsor(s)	Phase/Status/Comments
G, gatifloxacin, Tequin®	Fluoroquinolone	Bristol-Myers Squibb	Approved/marketed for some bacterial infections; status for TB unclear; may permit intermittent therapy (thrice weekly) and have activity against MDR-TB.
J, TMC207 (ex R207910)	Diarylquinoline	Tibotec/J&J	Phase I underway (dose-ranging studies); once- weekly dosing; may enable shortened duration of TB treatment; phase II discussions underway. Unique bactericidal mechanism; potential as MDR-TB treatment.
LL-3858	Pyrrole	Lupin Laboratories	India-based R&D manufacturer of cephalosporins, rifampin, etc.; has marketing offices in Maryland; unresponsive to queries for information.
M, moxifloxacin, Avelox®	Fluoroquinolone	Bayer	Marketed in 100+ countries for some bacterial infections; shown to reduce time for sterilization of TB-infected lungs and therefore has potential for shortening treatment time.
		Bayer/TBTC	Phase II underway for initial phase TB treatment (HRZM vs. HRZE; TBTC-27)
		Bayer/TBTC	Phase II in planning for use in the continuation phase of TB treatment (TBTC-28)
		Bayer/Global Alliance	Discussions underway between Bayer and Global Alliance regarding FDA IND (investigational new drug) application for M as TB drug.
PA-824	Nitroimidazopyran	Global Alliance for TB Drug Development	Active against active and static TB bacilli. Similar to R and H in sterilizing ability. Bactericidal activity against MDR-TB.
Proprietary Compound	Unknown	Otsuka Pharmaceuticals	Mystery compound from Japanese company; Otsuka not willing to share any information currently; compound is in clinical testing and information is to be released in September 2005 at the Interscience Conference on Antimicrobial Agents and Chemotherapy (IAAAC) in New Orleans, USA.

Table	1.	TB	Drugs	Currently	in	Clinical	Tria	s
and			2.480	Carrenty		Chinea		

Diarylquinoline TMC207 (J) (previously R207910)

This compound, TMC207, or J, is owned by Johnson & Johnson (J&J) and is being developed at its research subsidiary Tibotec. Tibotec scientists discovered J by screening their chemical libraries for compounds with anti-mycobacterial properties. The compound has many characteristics that make it an attractive TB drug candidate, including low molecular weight, high potency against drug-sensitive and drug-resistant TB strains, very long half-life (permitting once-weekly dosing), and low potential for drug interactions.

Mechanism: TMC207, or J, is among the Diarylquinoline (DARQ) class of compounds, which have a very specific and previously unknown anti-mycobacterial mechanism. It is postulated that J inhibits the proton pump of the M. tuberculosis adenosine triphosphate (ATP) synthase that is the main source of fuel for *M. tuberculosis* (Andries 2004).

Reduction of treatment burden: Studies in mice show that J has a long half-life (43.7–64.0 hours in plasma and 28.1–92.0 hours in tissue) and a low minimum inhibitory concentration (MIC). The bactericidal activity of the drug seems to be time-dependent, not concentration-dependent. Due to its ability to penetrate and stay concentrated in tissue for long periods of time, J holds the promise of being active against latent TB infection as well as active TB disease. Its long half-life, low MIC, and bactericidal potency also give J the potential to reduce the duration and the pill burden of TB treatment. In mice, a single dose had bactericidal potency for about eight days. When used as monotherapy, a single dose of J was at least as potent as the triple combination of rifampin (R), isoniazid (H), and pyrazinamide (Z) and was more active than R alone. Due to potential for resistance development, however, J will not be used as monotherapy, but only in combination with the other current TB drugs. When it was substituted for one of three current TB medications (R, H, or Z), the J-containing regimens performed significantly better—they were as effective in one month as RHZ was in two months. In particular, the JHZ and RJZ combinations cleared the lungs of TB in all the mice after two months. These promising murine data need to be replicated in humans (Andries 2004).

Utility against MDR-TB and TB/HIV coinfections: Because of its unique mechanism, J is active *in vitro* against TB organisms resistant to isoniazid (H), rifampin (R), streptomycin (S), ethambutol (E), pyrazinamide (Z), and moxifloxacin (M). Furthermore, it has no cross-resistance with current anti-TB medications (Andries 2004). J can be also be used in conjunction with antiretroviral drugs, and unlike rifampin, it doesn't accelerate their metabolism (Ibid.)

Adverse effects: Single ascending dose (SAD) and 14-day multiple ascending dose (MAD) studies in healthy human males were orally presented at the 16th TB Trials Consortium (TBTC) meeting in San Diego on 20 May 2005. J was well absorbed after a single oral dose and has an effective half-life of 24 hours. No severe adverse effects were observed. The treatment duration needed for sterilization, as well as the most effective drug combinations, are as yet unknown in mice and humans (McNeeley 2005).

Needed studies: Studies in TB patients have not yet begun. More research on the pharmacokinetics of the compound is needed to develop a safety profile in women, children, and individuals coinfected with HIV or HCV and TB. Studies that will provide more information about the sterilizing duration of the drug and its potential to prevent recurrence of TB still need to be conducted.

Fluoroquinolones

The fluoroquinolone (FQ) compounds are a class of synthetic antibiotic derived from nalidixic acid, with a broad spectrum of activity. This family includes ciprofloxacin and a variety of related compounds, two of which are in the current TB pipeline. FQs are well absorbed orally, and have good tissue penetration and relatively long duration of activity. Quinolones are "broad-spectrum antibacterial agents that block DNA replication and kill bacterial cells" (Drlica 2004). Some newer

fluoroquinolones are effective against nondividing bacteria as well; they do not have crossresistance to other classes of TB drugs. Several fluoroquinolones have been studied for their antimycobacterial activities (Pletz 2004; Gradelski 2002).

During the 1990s, two C-8-methoxy fluoroquinolones (moxifloxacin and gatifloxacin) were developed commercially for use against gram-positive pathogens... Moxifloxacin and gatifloxacin also had exceptional activity with *M. tuberculosis* if assessed by a mutant selection criterion. However, when examined for activity in cultured cells or in animal models, the C-8-methoxy compounds were not lethal enough to be spectacular anti-tuberculosis agents. Thus, successful use of fluoroquinolones with tuberculosis will probably require finding appropriate combination therapies (Drlica 2004).

Gatifloxacin (G)

Gatifloxacin is a broad-spectrum fluoroquinolone antibiotic that is marketed in the U.S. by Bristol-Myers Squibb as Tequin. It is used to treat a number of bacterial infections and is usually taken at 400 mg once daily (Bristol-Myers Squibb 2004).

Mechanism: An *in vitro* study looking at the bactericidal action of gatifloxacin (G) by itself and in combination with isoniazid (H) or rifampin (R) showed that G added limited bactericidal activity for the first two days, but not thereafter. The hypothesis is that G is active against the occasionally dividing bacteria, but that in the static, persisting bacilli it does not contribute any sterilizing activity to that of the other drugs (Paramasivan 2005).

Reduction of treatment burden: The failure of G to add to the sterilization activity of H or R suggests that it will not reduce treatment time. Gatifloxacin is active against intramacrophage *M. tuberculosis* when used with certain combinations of antituberculosis drugs (R, H, and Z). Gatifloxacin's activity against intramacrophage bacilli in combination with antituberculosis drug implies that with the right additional drugs, G can produce effective suppression of TB (Sato 2003). Another study looking at the use of G in combination with ethionamide (ETA) with or without pyrazinamide (Z) in mice showed that G, ETA, and Z was the most effective combination to sterilize the lungs and prevent relapse. When treated with G and ETA at 5 days/week doses of 300 mg/kg and 25 mg/kg of body weight, respectively, the mice lungs were completely sterilized in 12 weeks; however, there was relapse during the eight-week subsequent observation period. When Z was added to ETA and G at 450 mg/kg for 5 days/week for 12 weeks, the murine lungs remained free of live mycobacteria during eight weeks of follow-up observation. For the lower dose regimen of G at 300 mg/kg plus ETA at 75 mg/kg, the twice-weekly regimen was as effective as the daily regimen. These data suggest the possibility of using this regimen in intermittent therapy, thus potentially reducing treatment burden (Cynamon 2003).

Utility against MDR-TB and TB/HIV coinfections: As the above data show, gatifloxacin can be active in regimens without H or R. The combination of G, ETA, and Z could therefore potentially be useful against isoniazid- (H) and rifampin- (R) resistant TB. It is also anticipated that G will work well with ARVs (Cynamon 2003).

Adverse effects: None of the studies spoke of the any side effects specific to the treatment of TB; however, in general, fluoroquinolones can cause CNS toxicity. Gatifloxacin has been associated with increases in insulin levels among diabetics. Caution should be used when taking G along with antacids, heart rhythm disturbance medications, or with mineral supplements containing zinc, magnesium, or iron. Gatifloxacin has not been shown to be safe or effective in children younger than 18 or in pregnant or lactating women (Bristol-Myers Squibb 2004).

Needed studies: Studies are needed to more clearly define the use of G in combination with current TB therapy and to define its safety. The optimal dose and combination regimen for TB need to be understood better. The validity of the assumption that early sterilization of lungs is a predictor of relapse inhibition also needs to be studied.

Moxifloxacin (M)

Moxifloxacin (M) may be the most promising of the fluoroquinolones being tested against *M*. *tuberculosis* (Gillespie 1999). It is made by Bayer and marketed as Avelox (moxifloxacin hydrochloride) in over 100 countries for the treatment of a variety of bacterial infections. It is most often given as a single oral 400 mg dose once daily (Bayer 2004).

The bactericidal potential of M at 25 mg/kg six times a week was equivalent to isoniazid (H) (Ji 1998). A study in mice replicated this apparent equivalence between M and H monotherapy and also showed that the combination of M and H together is much stronger than each alone (Miyazaki 1999). M showed early bactericidal activity comparable to isoniazid and rifampin in human subjects (Pletz 2004; Gosling 2003).

Mechanism: M is a broad-spectrum antibiotic, active against gram-negative, gram-positive, and anaerobic bacteria. It has a mechanism that is distinct from H in that it affects bacteria by binding to the DNA gyrase and topisomerase IV, which are involved in bacterial replication. Compared to some other fluoroquinolones, it has a lower minimum inhibitory concentration (MIC) and a half-life that is equivalent to other fluoroquinolones. Unlike some other effective fluoroquinolones, M is not phototoxic (Ji 1998).

Reduction of treatment burden: Two studies in mice showed that using M along with already approved anti-TB drugs can lead to faster sterilization of the lungs. In mice, a combination of M along with rifampin (R) and pyrazinamide (Z) was shown to eradicate *M. tuberculosis* from the lungs by up to 2 months earlier compared to the standard regimen of isoniazid (H) with R and Z. Another study showed that adding M to a rifapentine and H regimen was more effective than adding streptomycin in clearing the lungs. Due to its sterilizing effect against slow or intermittent replicating bacteria, M in combination with other drugs seems promising for the continuation phase of TB treatment and to potentially shorten therapy (Lounis 2001). Some data from a yet unpublished study in mice that Jacques Grosset presented during the May 2005 TBTC meeting showed that four months of M with R and Z was as effective as six months of the standard regimen of RHZ/RH. In another study, TBTC Study 27 conducted by the CDC-funded TB Trials Consortium, unpublished data from a randomized, blinded comparison of HRZM vs. HRZE showed that the M-containing regimen led to faster sputum and culture-conversion, with no difference by dosing frequency (five versus three days weekly). However the study also showed

that there was a marked difference between African study participants and North American participants in the rates of two-month culture-conversion (60% vs. 85%; surprisingly, this difference was not affected by HIV status) (Burman 2005).

Utility against MDR-TB and TB/HIV coinfections: M might be very useful against MDR-TB since it has no cross-resistance to other antituberculosis drug classes. An *in vitro* pharmacodynamic infection model that simulated drug decline similar to those seen in humans suggested that doses of 400, 600, and 800 mg/day of M would suppress drug resistance in TB by 59%, 86%, and 93%, respectively (Gumbo 2004). When tested against 86 strains of *M. tuberculosis*, including 13 resistant and 4 multidrug-resistant ones, M was effective against all strains but two at 0.5 mcg/ml. The other two, both of which were MDR strains, were suppressed at minimum inhibitory concentration (MIC) of 2 and greater than 4 mcg/ml (Tortoli 2004). M plus ethionamide (ETH) showed more activity than M alone in mice infected with MDR-TB (Pletz 2004; Fattorini 2003).

When compared with the standard third-line regimen of ofloxacin (OFX), ethionamide (ETA), amikacin, and pyrazinamide (Z), nine months of M, ethionamide, amikacin, and Z was found to be as effective as six months of the standard third-line regimen. Thus, though it doesn't shorten the treatment, M does broaden the treatment options for MDR-TB (Veziris 2003).

M can be used with current ARVs, as it is a broad-spectrum antibiotic class that is already being prescribed commonly, and no drug interactions have been mentioned.

Adverse effects: M has CNS side effects and drug interactions with other FQs. Only small studies in TB patients have been done so far, and few AEs have been reported. Moxifloxacin has not been shown to be safe or effective in children younger than 18 or in pregnant or lactating women (Bayer 2004).

Needed studies: There is a need to better understand the pharmacokinetics of *M*, and to explain the potential ethnic or geographical differences in the two-month TB culture-conversion rates suggested in TBTC study 27. Moxifloxacin, like gatifloxacin, needs to have its safety and activity determined in children under 18 and in pregnant and lactating women. Finally, the role of *M* in combination therapy for TB, including initial intensive and continuation-phase regimens, and for treatment of MDR-TB and in combination with ARVs needs to be defined in well-conducted randomized and operational research studies.

Nitroimidazopyran PA-824

Since being identified in 1995 at PathoGenesis, this drug has had many proprietors. First Chiron Corporation acquired the compound and then the Global Alliance For TB Drug Development obtained worldwide rights to it and its derivatives from Chiron with Chiron's commitment to make the drug available for TB without royalty in countries where TB is endemic. *In vitro* and in murine models it is shown to be effective against MDR TB, and actively and slow growing *M. tuberculosis*.

Mechanism: PA-824 kills *M. tuberculosis* bacilli by inhibiting the synthesis of protein and cell wall lipids (Stover 2000). It has specific bactericidal effect against M. tuberculosis complex. In mice, it has a minimum bactericidal dose (MBD) of 100 mg/kg/day. When used at MBD by itself, PA-824

was bactericidal during initial therapy phase at a level comparable to an equipotent dose of isoniazid in humans (Tyagi 2005). It was even shown to be effective against MDR strains and TB bacilli grown under oxygen depletion showing potential bactericidal impact in latent state TB bacilli (Lenaerts 2005). Its sterilization effects rival those of R and H. PA-824 at a single oral dose of 25 and 100 mg/kg reached high levels in the lungs and spleen. Regular dosing over 14 days showed PA-824 was at higher levels in target tissues than in plasma and that the plasma concentration is dose dependent (Global Alliance 2004).

Reduction of treatment burden: In continuation phase PA-824 has been seen to target bacilli that had persisted despite a two-month intensive treatment phase of R, H, Z. There are no clear data that show the potential for PA-824 for shortening TB treatment. However, its effectiveness against active and static TB bacilli shows promise for its use in initial and continuing phases of TB treatment (Tyagi 2005).

Utility against MDR-TB and TB/HIV coinfections: PA-824 in combination with isoniazid prevents selection of TB mutants resistant to isoniazid (Tyagi 2005). Unlike current TB drugs, it has shown high bactericidal activity against all MDR-TB isolates as well as potential for activity against latent TB. There is no cause to suspect that PA-824 cannot be used with HIV medications as there was no significant inhibition of cytochrome P450 isozymes (Global Alliance 2004).

Adverse effects: The adverse effects profile of PA-824 has not yet been evaluated in humans.

Needed studies: Studies are needed to define PA-824's utility in TB treatment during the initial and continuation phase for drug-susceptible TB infections, and its best use in combination for MDR-TB. Clinical trials are needed to define its adverse effects profile, its sterilization effect, and its effect on TB culture conversion and on preventing relapse. Since it seems active against MDR-TB, its use needs to be defined in hepatitis C virus (HCV) and HIV coinfected TB patients.

Otsuka Pharmaceuticals and Lupin Laboratory Compounds

Two additional drugs are also currently being tested in the clinic: a proprietary compound of Otsuka Pharmaceuticals, and pyrrole LL-3858 of Lupin Laboratories. Currently, there is no significant information publicly available about these compounds.

Conclusions

As the above pipeline shows, it is an exciting time for TB drug development. There is the promise of therapies that may shorten treatment duration of drug-susceptible TB, as well as increase treatment options for MDR-TB. The novel mechanism of activity and long half-life of TMC207, or J, has promise for not only reducing treatment burden, but also providing a powerful tool against TB that is resistant to current TB drugs. The sterilizing effects of M and G have the potential to reduce time to culture-conversion, thereby reducing the transmission and potential for relapse.

Much work remains to be done, however, before these drugs can be adopted into standard regimens. This work includes better understanding drug dosage and drug interactions, and developing a safety profile for these drugs. New trial designs need to be devised as well as rapid,

well-designed, well-controlled studies for these drugs to make a difference in reducing the world's TB and TB/HIV epidemics in the near future. Researchers, study sponsors, and regulatory agencies including the Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA) need to agree on study designs that can quickly validate these new TB drugs while also defining their side effects and potential interactions with ARVs and other commonly used drugs. FDA should consider utilizing accelerated approval mechanisms for TB drugs that fill unmet needs in TB control.

TAG is concerned that there is insufficient infrastructure worldwide to rapidly validate these new TB drugs and scale up their use in a variety of settings where they will be needed. The only well-established multicenter network capable of carrying out clinical trials of new TB drugs, the CDC-funded TB Trials Consortium (TBTC), receives just \$9.2 million in funds annually and will experience a budget cut of \$800,000 due to reduced federal support for the CDC. Though in its recent trials the TBTC has added well-performing and highly productive international sites in Brazil, South Africa, and Uganda, TBTC is mainly centered in North America, where TB case rates are still falling. There is an urgent need to further expand the TBTC significantly to enhance its capacity to carry out the larger, longer, phase III studies that will soon be needed to validate the efficacy of the new anti-TB drugs. Much broader support is also needed from the National Institutes of Health (NIH) for clinical trials of new TB drugs. Other consortia approaches like the new European and Developing Country Clinical Trials Program (EDCTP) are also needed and require funding well in excess of its current budget of \$400 million for 5 years (2003–2008) for HIV, TB, and malaria. The U.K. Department for International Development (DFID) could also provide significant new support along with other developed and developing countries. Additionally, the human resources and insights of affected communities and people with TB are still untapped. Their leadership is vital to further TB treatment and advocacy and will also be needed to make TB trials a success.

Based on the current prediction of resources, the draft plan of the New Drugs Working Group for the Global Plan to Stop TB II anticipates that the first new TB drugs will be available by 2010 at the earliest. Dramatically scaled-up funding for clinical trials of new TB drugs will be a prerequisite for achieving success. High-level political will and significant resources must be mobilized to accelerate these developments lest the unconscionable deaths of two million people continue unabated year after year.

References

Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of Mycobacterium tuberculosis. Science. 2005 Jan 14;307(5707):223-7.

Bayer. Avelox® (moxifloxacin hydrochloride) package insert. Revised 2004. www.avelox.com, accessed 25 May 2005.

Bristol-Myers Squibb. Tequin® (gatifloxacin) tablets. November 2004. www.tequin.com, accessed 25 May 2005.

Burman W. First report: results from study 27 (oral presentation). TBTC 17th Semi-Annual Group Meeting, San Diego, CA, 20 May 2005.

Chauhan LS, Arora VK; Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare; Indian Academy of Pediatrics. Management of pediatric tuberculosis under the Revised National Tuberculosis Control Program (RNTCP). Indian Pediatr. 2004 Sep;41(9):901-5.

Cynamon MH, Sklaney M. Gatifloxacin and ethionamide as the foundation for therapy of tuberculosis. Antimicrob Agents Chemother. 2003 Aug;47(8):2442-4.

Drlica K, Lu T, Malik M, Zhao X. Fluoroquinolones as antituberculosis agents. Chapter 53 in Rom WN, Garay SM, Tuberculosis, 2nd edition, Lippincott Williams & Wilkins (2004), 791-806.

Fattorini L, Tan D, Iona E, et al. Activities of moxifloxacin alone and in combination with other antimicrobial agents against multidrug-resistant Mycobacterium tuberculosis infection in BALB/c mice. Antimicrob Agents Chemother. 2003 Jan;47(1):360-2.

Gillespie SH, Billington O. Activity of moxifloxacin against mycobacteria. J Antimicrob Chemother. 1999 Sep;44(3):393-5.

Global Alliance for TB Drug Development. Fact Sheet on PA-824. Oct 2004.

Global Partnership To Stop TB. Global Plan to Stop TB I. 2000, 17-30.

Gosling RD, Uiso LO, Sam NE, et al. The bactericidal activity of moxifloxacin in patients with pulmonary tuberculosis. Am J Respir Crit Care Med. 2003 Dec 1;168(11):1342-5.

Gradelski E, Kolek B, Bonner D, Fung-Tomc J. Bactericidal mechanism of gatifloxacin compared with other quinolones. J Antimicrob Chemother. 2002 Jan;49(1):185-8.

Grosset J. The least of them all: murine studies (oral presentation). TBTC 17th Semi-Annual Group Meeting, San Diego, CA, 20 May 2005.

Gumbo T, Louie A, Deziel MR, Parsons LM, Salfinger M, Drusano GL. Selection of a moxifloxacin dose that suppresses drug resistance in Mycobacterium tuberculosis, by use of an *in vitro* pharmacodynamic infection model and mathematical modeling. J Infect Dis. 2004 Nov 1;190(9):1642-51.

Harries A- a. What are the current recommendations for standard regimens? Chapter 25 in T. Frieden, Toman's Tuberculosis, 2nd Edition, World Health Organization (2004), 124-128.

Harries A- b. What are the most common adverse drug events to first-line tuberculosis drugs, and what is the procedure for reintroduction of drugs? Chapter 31 in T. Frieden, Toman's Tuberculosis, 2nd Edition, World Health Organization (2004), 152-159.

Ji B, Lounis N, Maslo C, Truffot-Pernot C, Bonnafous P, Grosset J. *In vitro* and *in vivo* activities of moxifloxacin and clinafloxacin against Mycobacterium tuberculosis. Antimicrob Agents Chemother. 1998 Aug;42(8):2066-9.

Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. Lancet. 2004 Oct 2;364(9441):1244-51.

Lenaerts AJ, Gruppo V, Marietta KS, et al. Preclinical testing of the nitroimidazopyran PA-824 for activity against Mycobacterium tuberculosis in a series of *in vitro* and *in vivo* models. Antimicrob Agents Chemother. 2005 Jun;49(6):2294-301.

Lounis N, Bentoucha A, Truffot-Pernot C, et al. Effectiveness of once-weekly rifapentine and moxifloxacin regimens against Mycobacterium tuberculosis in mice. Antimicrob Agents Chemother. 2001 Dec;45(12):3482-6.

McNeeley D, Cavaleri M. TMC 207 oral presentation. TBTC 17th Semi-Annual Group Meeting, San Diego, CA, 20 May 2005.

Médicins Sans Frontières. Running out of breath: TB care in the 21st century. March 2005.

New Drugs Working Group of the Stop TB Partnership. Draft of New Drugs chapter for Global Plan to Stop TB-II. May 2005.

Paramasivan CN, Sulochana S, Kubendiran G, Venkatesan P, Mitchison DA. Bactericidal action of gatifloxacin, rifampin, and isoniazid on logarithmic- and stationary-phase cultures of Mycobacterium tuberculosis. Antimicrob Agents Chemother. 2005 Feb;49(2):627-31.

Pletz MW, De Roux A, Roth A, Neumann KH, Mauch H, Lode H. Early bactericidal activity of moxifloxacin in treatment of pulmonary tuberculosis: a prospective, randomized study. Antimicrob Agents Chemother. 2004 Mar;48(3):780-2.

Sato K, Tomioka H, Sano C, et al. Comparative antimicrobial activities of gatifloxacin, sitafloxacin and levofloxacin against Mycobacterium tuberculosis replicating within Mono Mac 6 human macrophage and A-549 type II alveolar cell lines. J Antimicrob Chemother. 2003 Aug;52(2):199-203.

Stover CK, Warrener P, VanDevanter DR, et al. A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis. Nature. 2000 Jun 22;405(6789):962-6.

Tortoli E, Dionisio D, Fabbri C. Evaluation of moxifloxacin activity *in vitro* against Mycobacterium tuberculosis, including resistant and multidrug-resistant strains. J Chemother. 2004 Aug;16(4):334-6.

Tyagi S, Nuermberger E, Yoshimatsu T, et al. Bactericidal activity of the nitroimidazopyran PA-824 in a murine model of tuberculosis. Antimicrob Agents Chemother. 2005 Jun;49(6):2289-93.

Veziris N, Truffot-Pernot C, Aubry A, Jarlier V, Lounis N. Fluoroquinolone-containing third-line regimen against Mycobacterium tuberculosis *in vivo*. Antimicrob Agents Chemother. 2003 Oct;47(10):3117-22.

World Health Organization, Europe. The tuberculosis challenge in the European region. Fact Sheet EURO/01/04. March 2004.

TΔG

P-1212 • BMS-378806 • Mifepristone • JTK-303 (GS 9137) • L-870812 • DOT • dioxolan 873140 • PA-457 • SPD-754 • Elvucitabine (ACH-126) • TMC-125 (etravirine) • PRO-54 /icriviroc (SCH 417, SCH D) • TNX-355 • TMC-114/r • ALVAC vCP1521 • AIDSVAX B/E • I accine • VRC-HIVADV014-00-VP • AdVax 101 (VEE) • VRC-HIVDNA016-00-VP • TBC-M358 24 • HIV CTL MEP • DNA + Protein Vaccine Combination • tgAAC09 AAV • ADVAX DNA • EP HIV-1090 DNA • Carraguard • Cellulose sulfate (Ushercell) • PRO 2000/5 Gel • S enofovir/PMPA Gel • Invisible Condom • ACIDFORM Gel • Cellulose acetate 1,2-benzenec el) • ALVAC (vCP1452) • Lipopeptides • VRC-HIVDNA009-00-VP • MVA-BN-nef • MVA-mE accination w/conserved HIV-derived peptides • Multi-epitope DNA • DNA/MVA • Remune + eginterferon alfa-2a) • BAY 50-4798 • HRG214 Passive Immunotherapy • Interleukin-7 (IL-7 enapax (daclizumab) • CD4zeta modified CD4 and CD8 T cells • Ribozymes (RRz2) • VRX4 CV-796 • Merimepodib (VX-497) • Viramidine • IDN-6556 • Omega Interferon • DUROS i ANA975 (oral) • Actilon (CPG 10101) • Zadaxin (thymosin alpha 1; thymalfasin) • G, gati