



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

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PRO2000/5 gel • Savvy • ALVAC (vCP1521) • ALVAC (vCP1452) • MRKAd5 • lime juice
consensus interferon • Viramidine • valopicitabine • rilpivirine • TMC120 • GI262570
BMS-378806 • brecanavir/r • bevirimat • killed mycobacterium vaccae (SRL172) • valproic acid
Locteron-interferon • GS 9132/ACH 806 • HCV-796 • vicriviroc • Sudoterb • Racivir
bavituximab • MVA-85^a • XTL-6865 • GSK364735 • TAK-652 • HGS004 • BILR 355/r • GS-9132
(M) • gatifloxacin (G) • Tenofovir • Carraguard • cellulose sulfate • PRO2000/5 gel • Savvy
PRO-140 • etravirine • TNX-355 • TMC 207 (J) • PA-824 • Albuferon • consensus interfe
Pegasys • cyclosporine A • IDN 6656 • KP-1461 • PPL-100 • BMS-378806 • brecanavir
peptides • R1626 • XTL 2125 • rBCG::D • celgosivir • rBCG30 • Actilon • Locteron-interfe
abine • TMC278 • apricitabine • AMD-070 • Civacir • BI-201 • bavituximab • MVA-85^a • XT
VivaGel • invisible condom • BufferGel • maraviroc • moxifloxacin (M) • gatifloxacin (G)
ALVAC (vCP1452) • MRKAd5 • lime juice • VX-950 • SCH 503034 • PRO-140 • etraviri
picitabine • rilpivirine • TMC120 • GI262570 • interleukin-2 • Pegasys • cyclosporine

Hepatitis C Virus (HCV) Drug and Vaccine Pipeline 2006

by Tracy Swan

Hepatitis C: Scope of the Problem

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

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

HIV/HCV Coinfection

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

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

Current HCV Therapy

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

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

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

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

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

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

Desirable Elements for Future Therapies

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

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

The Clinical Pipeline

Get Down and Stay Down: Antiviral Agents

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

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

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

Hepatitis C Protease Inhibitors

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

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

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

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

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

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

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

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

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

Dosing, Boosting and Resistance

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

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

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

Hepatitis C Polymerase Inhibitors

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

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

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

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

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

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

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

Hepatitis C Alpha-Glucosidase Inhibitors

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

Immunomodulators

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

Toll-like Receptor Agonists

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

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

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

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

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

New Formulations and Types of Interferon

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

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

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

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

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

Mono- and Polyclonal Antibodies

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

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

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

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

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

Preventive and Therapeutic Vaccines

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

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

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

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

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

There is evidence for a preventive hepatitis C vaccine in chimpanzees. Folgari and colleagues reported that a vaccine made from DNA coding of the hepatitis C nonstructural region elicited cellular immune responses that prevented chimpanzees with acute HCV from developing chronic infections (Folgari 2006).

Chiron has developed a vaccine made from hepatitis C envelope glycoproteins that is currently in phase I. In earlier trials, Chiron's HCV vaccine candidate prevented chronic HCV infection via cellular and humoral immune responses in a majority of chimpanzees challenged with a homologous virus (Houghton 2005; Abrignani). Chiron is hoping to have a preventive vaccine candidate approved by 2010.

Anti-Fibrotic Agents

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

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

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

could not tolerate or respond to HCV treatment.

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

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

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

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

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

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

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

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

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

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

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

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

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

Interferon Enhancer?

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

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

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

Research & Policy Issues

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

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

Several research issues warrant consideration from regulators and the community:

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

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

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

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

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

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

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

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

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

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

Guide me!

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

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

Deliver Me!

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

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

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

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

On-line Resources: Treatment Guidelines

(Accessed on 10th June 2006)

American Association for the Study of Liver Diseases
Practice Guideline: Diagnosis, Management and Treatment of Hepatitis C
www.aasld.org/eweb/docs/hepatitisc.pdf

British HIV Association (BHIVA)
Guidelines for treatment and management of HIV and Hepatitis C coinfection
www.bhiva.org/guidelines/2004/HCV/indexmfrm.html

National Institutes of Health Consensus Conference Statement
<http://consensus.nih.gov/2002/2002HepatitisC2002116html.htm>

First European Consensus Conference on the Treatment of Chronic Hepatitis B and C in HIV Co-Infected Patients
Short Statement
www.jhepelsevier.com/article/PIIS016882780500142X/abstract

US Department of Health and Human Services
Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents
www.aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?MenuItem=Guidelines&Search=Off&GuidelineID=7&ClassID=1

Veterans Affairs National Hepatitis C Program
Treatment Recommendations for Patients with Chronic Hepatitis C, September 2003, v.5
www.hepatitis.va.gov/vahep?page=tp03-01-04-01

Veterans Affairs National Hepatitis C Program
Management and Treatment of Hepatitis C Virus Infection in HIV-Infected Adults
www.hepatitis.va.gov/vahep?page=tp04-gd-01

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

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

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

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