



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

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e thymidine • BI-201 • Racivir (PSI 5004) • TMC-278 • Diarylpyrimidine (DAPY) • 640385
• Reverset (D-D4FC) • JTK-303 • UK-427 (maraviroc) • Amdoxovir • AMD-070 • Vicriviroc
LIPO-5 • GTU-Multi-HIV • pHIS-HIV-B • rFPV-HIV-B • ADMVA • GSK Protein HIV Vaccine
TBC-M335 (MVA) • TBC-F357 (FPV) • TBC-F349 (FPV) • LIPO-4T (LPHIV-1) • LFn-p24 • H
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
ulose acetate/CAP) • Lime Juice • TMC120 • UC-781 • VivaGel (SPL7013 gel) • ALVAC
Ad5 • Autologous dendritic cells pulsed w/ALVAC • Autologous dendritic cell HIV vaccination
x • Tat vaccine • GTU-nef DNA vaccine • Interleukin-2 (IL-2) • HE2000 • Pegasys (peginter
L-4/IL-13 trap • Serostim • Tucaresol • MDX-010 anti-CTLA4 antibody • Cyclosporine A •
96 • HGTV43 • M87o • Vertex • VX-950 • Idenix • Valopicitabine (NM283) • JTK-003
implant • Albuferon • Celgosivir (MBI-3253) • IC41 • INN0101 • Tarvicin • ANA971 (oral)
floxacin, Tequin • J, TMC207 (ex R207910) • LL-3858 • M, moxifloxacin, Avelox • PA-824

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 once-weekly 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.

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

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)

* 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 thrombocytopenia) 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 coinfecting persons than for those with HCV mono-infection (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 coinfecting 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 coinfecting 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 coinfecting 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-coinfecting 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.

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

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)		
<i>Idenix</i> Valopicitabine (NM283)	Phase IIa	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 IIa study has been extended to 48 weeks; so far, data to week 24 are available.
<i>Japan Tobacco</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 C IMPDH (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 Caspase Inhibitors (oral)		
<i>Pfizer/dun pharmaceuticals</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 Formulations of Interferon (injection; subcutaneous infusion/implant)		
<i>Intarcia Therapeutics</i> 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 IIb	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 events 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 IIa	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 Vaccines		
<i>Intercell</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>Innogenetics</i> INN0101	Phase I/IIb	Uses HCV genotype 1b envelope protein (E1) to elicit immune response. Phase I/II: safety, efficacy, and tolerability of INN0101 expressed in yeast in 122 volunteers with hepatitis C; results expected at the end of 2005. A phase IIb evaluation of the effect of INN0101 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 Antibodies (infusion)		
<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)		
<i>Anadys</i> ANA971 (oral) <i>Anadys/Novartis</i> 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.
<i>SciClone</i> <i>Pharmaceuticals</i> 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 non-responders 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.

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