

Antivirals—an increasingly healthy investment

Brian McCarthy

Continued investment from big pharma and a slew of new drugs with novel mechanisms of action are fueling investor interest in the antiviral space.

The antiviral sector offers unmet medical needs, large patient markets, suboptimal standards of care and substantial profits for successful drug candidates. It is an area where biotech companies that advance drug candidates into clinical development can attract pharmaceutical partners. And it continues to be a major focus for biotech companies—in terms of the number of biopharmaceuticals, it is second only to cancer. Here, four main trends—new mechanisms, second-generation molecules, combination treatments and novel administration routes—in the antiviral market are highlighted along with some of the novel drug candidates that are attracting investor attention.

The market opportunity

The number of approved antiviral drugs has increased substantially during the past decade. Fueled by the constant threat of drug resistance, lower-than-desired cure rates and the need for drugs that offer improved quality of life during treatment, in the coming years, the worldwide antiviral market is estimated to grow from ~\$18 billion to as much as \$25 billion by 2011 (ref. 1). The leading drugs for this market have been treatments for human immunodeficiency virus (HIV) and the hepatitis B and C viruses (HBV, HCV), which have generated annual sales of nearly \$8.5 billion and \$3.8 billion, respec-

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tively² (Fig. 1). Several mainline antiviral drugs have or will go off-patent, including reverse transcriptase inhibitors, such as Gilead's (Foster City, CA, USA) Emtriva (emtricitabine), Bristol-Myers Squibb's (Princeton, NJ, USA) Videx (didanosine), GlaxoSmithKline's (London) Ziagen (abacavir sulfate) and Combivir (lamivudine/zidovudine), as well as first-line protease inhibitors, such as Hoffmann-La Roche's (Basel) Invirase/Fortovase (saquinavir) (see Table 1). In spite of imminent generic competition, the arrival of 'next-generation' and 'first-in-class' drugs is still expected to generate double-digit market growth.

The constant need to refill the antiviral drug pipeline to keep up with the emergence of viral resistance also represents an opportunity for biotech firms. For many viruses, especially HIV and HCV, rapid viral adaptation and drug resistance render many existing treatments ineffective with repeated use. Although viral adaptation can affect the market share for established drugs, it also creates the potential for new drugs to enter the market. To address this need, several biotech companies are advancing drug candidates with new methods of action, such as Alnylam's (Cambridge, MA, USA) RNA interference (RNAi) technology, Idera Pharmaceutical's (Cambridge, MA, USA) Toll-like receptor (TLR)-9 agonists or Hemispherx Biopharma's (Philadelphia) Ampligen (immunostimulatory double-stranded RNA), which activates TLR-3. Antiviral drug development is thus focusing not only on viral targets (e.g., HIV reverse transcriptase or protease) but also on host-cell specific targets, offering new paths for blocking the progression of infection.

Factors driving antiviral investment

Investors actively pursue drug candidates for viral diseases that offer large patient markets, chronic pathologies requiring long-term treatment, patient demographics in the developed as opposed to third world, and rapid acceptance by physicians and drug formularies.

As a result of the above, to date, most antiviral drug development has been directed toward HIV, HBV, HCV and the herpes viruses. Investors are particularly attracted to unmet medical needs within the antiviral space where existing therapies fail to provide adequate cure rates or quality of life. Although investors are attracted to chronic pathologies requiring long-term treatment, acute viral infections (e.g., influenza) are gaining ground where much biotech effort is devoted toward promising prophylactic vaccines. For programs seeking government funding (e.g., biodefense), however, some investors remain cautious because of

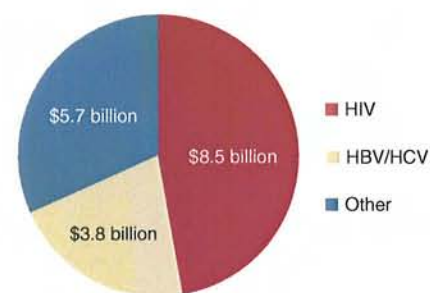


Figure 1 The antiviral market. The antiviral market is currently valued near \$18 billion, with the largest submarkets comprising drugs for the treatment of HIV and the hepatitis viruses. Dollar amounts are in billions.

perceived uncertainties surrounding federal contracts.

Investments are thus focusing on treatments with new mechanisms of action, second-generation versions of existing molecules with improved pharmacokinetic or pharmacodynamic profiles, combinations of new agents with existing therapies to address viral resistance and drugs administered by new (topical) routes. One area that exemplifies progress in these areas is HCV treatment, which is discussed in more detail below.

New mechanisms of action

HCV remains one of the antiviral market's largest unmet medical needs. Because of extensive HCV sequence diversity, it has been difficult to develop an effective prophylactic vaccine against the virus. The current standard-of-care treatment for the disease—interferon (IFN)- α in combination with the nucleoside analog ribavirin—is suboptimal; administered once-a-week by injection, these drugs are not well tolerated by many individuals and often cause side effects. Depending on the specific HCV genotype, as little as one-half of those treated can expect a cure. This has added urgency to the search for new drugs with alternative mechanisms that might have greater efficacy and fewer side effects.

Several biotech companies, such as Vertex Pharmaceuticals (Cambridge, MA, USA), Enanta Pharmaceuticals (Watertown, PA, USA), VGX Pharmaceuticals (Blue Bell, PA, USA) and Debiopharm (Lausanne, Switzerland) are pursuing HCV drug candidates with new mechanisms. First-in-class drugs are actively pursued by investors because their novel mechanisms of action can offer greater specificity, more targeted action, improved market penetration and patent protection, more favorable side-effect profiles and synergistic administration—not to mention a technological jump start on the competition.

Novel approaches against HCV include candidates that block viral RNA replication by targeting the polymerase enzyme, inhibit viral protein cleavage by targeting the HCV protease, stimulate the immune system to better fight HCV infection, exploit RNAi to slow the production of viral proteins and use biologics to target viral components.

Several biotech firms, including Pharmasset (Princeton, NJ, USA) and Gilead, have pursued the development of nucleoside and nonnucleoside drugs targeting HCV polymerase, in the knowledge that intervening at a similar point in the HIV lifecycle has proven successful in the past.

Table 1 HIV therapeutics with recent or imminent patent expirations

Company	Drug (generic name)	Patent	Date of expiration
<i>Nucleoside analog reverse transcriptase inhibitor</i>			
Bristol-Myers Squibb	Videx (dideoxyinosine)	US 5,254,539	March 2007
Bristol-Myers Squibb	Zerit (stavudine; d4T)	Various	June 2008
Glaxo Wellcome	Ziagen (abacavir)	Various	June–December 2009
Glaxo Wellcome	Combivir (lamivudine/zidovudine)	US 5,859,021	May 2012
Gilead	Emtriva (emtricitabine)	US 5,210,085	July 2008
Hoffmann-La Roche	Zalcitabine (ddC)	Various	July 2008
<i>Protease inhibitor</i>			
Hoffmann-La Roche	Invirase/Fortovase (saquinavir mesylate)	US 5,196,438	November 2010

Optimism that a successful HCV polymerase inhibitor candidate may soon enter the market has, however, been dampened by two recent clinical setbacks (see article p. 1379).

Nevertheless, at the 2007 Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) in early November, the HCV polymerase inhibitor space got a boost with positive clinical news from Pharmasset. In collaboration with Hoffmann-La Roche (Basel), the company announced results from a phase 1 monotherapy study showing that its small-molecule polymerase inhibitor candidate (R7128) demonstrated a >99% mean decrease in HCV RNA, with no serious adverse events. R7128 has been shown to produce dose-dependent suppression of HCV replication.

Another viral target, the HCV NS3-4A serine protease, has also been the focus of several development programs and is being closely tracked by investors. With candidates in phase 2 clinical evaluation, Schering-Plough (Kenilworth, NJ, USA) and Vertex Pharmaceuticals (Cambridge, MA, USA) both hope to be the first to market with an HCV protease inhibitor that can improve the current 50% cure rate of IFN- α and ribavirin. Last April, Vertex announced encouraging data from the company's ongoing phase 2b clinical trial of telaprevir (VX-950), followed by Schering's report of encouraging results for their protease inhibitor boceprevir in October.

Presentations at AASLD highlighted the fierce competition within the HCV protease inhibitor space. Vertex took a hit from investors after Schering presented data on its small molecule, boceprevir, indicating it achieved undetectable HCV RNA in up to 79% of patients (up from 50% expected cure rate with standard ribavirin and IFN- α treatment) in combination with the established standard of care for HCV. The fact that Vertex's telaprevir was reported at the

same meeting to produce undetectable HCV RNA in 61% of patients in combination with existing therapies was overlooked amid investor concern over Vertex's trial dropout rates and telaprevir's potentially problematic side-effect profiles compared with Schering's drug. Investors reacted strongly, perceiving that telaprevir may face greater-than-expected competition from rival therapies.

IFN- α 2b has been a stalwart of HCV therapy for over a decade. Because of the prevalence of viral adaptation and drug resistance, it is anticipated that immunomodulators such as IFN- α 2b will remain a necessary part of HCV treatment. This is fueling investor interest in new therapies that stimulate the host's immune system to fight infection. These novel approaches include several different molecules that stimulate TLRs, as well as a therapeutic HCV vaccine (see **Box 1**). TLRs serve an important role in normal immune function, where they recognize invading pathogens and organize an immune response. In particular, HCV has evolved mechanisms to aid its own pathogenesis by interfering with the signaling of at least one TLR (TLR-3). Nevertheless, it has not been plain sailing in the clinic as companies learn to optimize immune modulation and minimize side effects not encountered with direct antivirals. In January, Coley Pharmaceuticals (Wellesley, MA, USA) suspended clinical development of its CpG oligonucleotide TLR9 agonist (Actilon; CPG 10101) after it failed in phase 2 to show meaningful HCV viral load reduction in nonresponder patients. Soon after in July, after unfavorable animal toxicology results, Anadys Pharmaceuticals (San Diego) and Novartis (Basel) also announced discontinuation of a phase 1b clinical study evaluating the isatoribine oral pro-drug (ANA975), a TLR-7 agonist for HCV.

Despite these setbacks, a potentially more effective TLR contender recently entered

Box 1 Focusing on vaccines rather than therapies

In contrast to recent successes with HIV therapeutics, the development of a prophylactic HIV vaccine has proven challenging. After years of HIV research, investigators have identified specific immune responses that they believe to be important in fighting HIV. In particular, research points to a role for CD8⁺ T lymphocytes in the suppression of viral replication and in the control of HIV infection. This is supported by studies showing that CD8⁺ T-lymphocyte responses correlate with HIV resistance in some patients. Vaccines that maximize HIV-specific CD8⁺ T-cell responses have entered clinical development; however, designing a vaccine that prevents HIV infection continues to prove challenging.

A major blow to the community came on September 21, when an independent Data Safety Monitoring Board recommended discontinuation of a phase 2 clinical trial of Merck's V520 HIV vaccine (a trivalent vaccine of *gag*, *pol* and *nef*) after interim analysis showed that the vaccine would not likely prevent HIV infection or reduce viral load. As a result, the approaches of two biotech companies, Vical (San Diego, CA, USA) and GenVec (Gaithersburg, MD, USA), are gaining investor attention.

The Vaccine Research Center at the National Institutes of Health (NIH) is advancing a 'prime/boost' vaccine that incorporates the plasmid DNA technology of Vical to prime the immune system and

the adenoviral vector technology of GenVec for an immune booster step. Both the prime and boost portions of the vaccine deliver genes encoding three HIV proteins (*gag*, *pol* and *env*), whereas the DNA prime also incorporates the gene encoding the viral nef protein. Encouraging results from a series of phase 2a clinical trials showed that the DNA prime/adenoviral boost vaccine induces T-cell immune responses in up to 70% of subjects.

Fueling hopes that the NIH's vaccine will be more effective than Merck's V520, the NIH vaccine (i) incorporates a fourth protein (*env*) known to be important in HIV infection, (ii) includes *env* genes from all three major HIV subtypes and (iii) uses a heterologous DNA prime/adenoviral boost combination that enables multiple priming and produces both strong CD4⁺ and CD8⁺ T-lymphocyte immune responses.

In the field of HCV vaccines, there is also progress. One example is Intercell's (Vienna) IC41—five synthetic peptides from different regions of the HCV polypeptide containing three T-cell epitopes and the company's proprietary poly-L-arginine-based TLR adjuvant. Investors took note of the company's recent encouraging phase 2 interim results (released in August) showing that IC41 produced a small and sustained, statistically significant reduction in viral load. Final results are expected early next year.

clinical trials for HCV. IMO-2125 is a novel synthetic DNA-based TLR-9 agonist, where natural cytosine and guanine (within CpG dinucleotide motifs) have been substituted with synthetic pyrimidine and purine bases. Under development by Idera Pharmaceuticals, IMO-2125 has demonstrated encouraging preclinical results and is more effective than some previous compounds in stimulating the release of IFN- α and interleukin-2 in nonhuman primates. On the basis of these findings, in September Idera initiated a phase 1 study to evaluate the safety of IMO-2125 in HCV patients who have not responded to standard-of-care combination therapy. The trial is also anticipated to provide some preliminary information regarding IMO-2125's effect on HCV RNA levels and immune system activation.

Another area that has dominated the headlines in recent years is RNAi. At the forefront of the RNAi clinical race is a phase 2 antiviral candidate that is attempting proof of concept in humans. Developed for the treatment of respiratory syncytial virus (RSV), ALN-RSV01 has been advanced by Alnylam Pharmaceuticals (Cambridge, MA, USA) to block viral replication by interfering with an mRNA that encodes the virus's nucleocapsid protein. Facilitated by aerosol delivery to lung tissue, ALN-RSV01 has moved into a phase 2 trial (initiated in June) to evaluate safety, tolerability and antiviral activity in RSV-infected patients, with data expected in late 2007. Although other RNAi clinical

programs are focused outside the antiviral space, efforts to develop additional antiviral RNAi therapies are progressing toward the clinic. One example, Tacere Therapeutics (San Jose), is moving toward the lucrative HCV space with an RNAi therapy (TT-033) that targets three regions of the HCV genome with a high degree of homology across viral genotypes.

A final area that is increasing in prominence—on the heels of the success of targeted biopharmaceuticals in oncology—is the use of biologics, specifically monoclonal antibodies (mAbs) and polyclonal antibodies, as antivirals. Although biologics are driving growth in some disease markets, antiviral biologic development has been slow because of the success of high-throughput screens in identifying potential small-molecule regulators of HCV replication and the minimal viral reduction observed with early-stage biologic candidates. Even so, Peregrine Pharmaceuticals (Tustin, CA, USA) is developing bavituximab, which targets aminophospholipids on the surface of HCV-infected cells. The company announced phase 1b results at AASLD, demonstrating that the chimeric mAb is well tolerated in patients and produces antiviral activity at all doses.

Pursuing niche markets, Nabi Biopharmaceuticals (Boca Raton, FL, USA) is developing Civacir, a preparation of polyclonal antibodies, for prevention of HCV recurrence in liver transplant recipients. Currently in phase 2,

results of a previous phase 1/2 trial showed Civacir to be well-tolerated and reduce a key liver enzyme, although HCV RNA levels in serum were not suppressed. In addition, XTL Biopharmaceuticals (Valley Cottage, NY, USA) is developing XTL-6865, a combination of two fully human mAbs (Ab68 and Ab65) that target the HCV E2 envelope protein. Phase 1 results showed XTL-6865 to be safe but not to have an effect on HCV RNA levels during the trial's short administration period. XTL is expected to evaluate XTL-6865 in individuals with hepatitis C undergoing liver transplantation and to seek partnerships for future clinical development.

Second-generation molecules

The need to improve quality of life for patients on the existing antiviral regimens has driven industry efforts to develop second-generation molecules with improved pharmacokinetics and pharmacodynamics. Biotech companies, such as Human Genome Sciences (Rockville, MD, USA) and Biolex Therapeutics (Pittsboro, NC, USA), are evaluating several enhanced IFN- α candidates that offer reduced side-effect profiles and fewer injections.

For example, many investors are closely watching Albuferon, a long-acting form of IFN- α 2b genetically fused to human albumin in phase 3 clinical evaluation by Human Genome Sciences (see p. 1411). At AASLD last month, Albuferon showed an acceptable

safety profile and produced a 17% sustained virologic response rate, in combination with ribavirin, in individuals with HCV who failed to respond to previous pegylated IFN and ribavirin therapy. Another candidate, Locteron—a controlled-release formulation in which IFN- α 2b is encapsulated in biodegradable poly(ether ester) multiblock copolymers based on poly(ethylene glycol) and poly(butylene terephthalate)—is in phase 2a evaluation by Biorex Therapeutics. Data reported at AASLD showed that Locteron produced antiviral activity and a favorable side-effect profile when administered every 2 weeks to treatment-naive individuals with chronic type-1 HCV.

Combination therapies

Combination therapies have been a great success in HIV, and are growing in popularity for oncology. As HIV and HCV display a significant degree of viral adaptation and rapid drug resistance, investors anticipate that future therapies will incorporate new combinations of antivirals. Another upside of this approach is that drugs clinically proven to be synergistic in combination with existing therapies can be better positioned to gain physician approval and achieve market penetration by minimizing the paradigm shift required of physicians.

One example of a development program planning to exploit this strategy is that of Pharmasset and Roche, which is currently enrolling subjects in a phase 1 clinical evaluation of R7128 as a combination therapy for treatment-naive HCV-1 patients. And R7128 is not the only HCV polymerase inhibitor being pursued as a combination therapy. Roche's rival polymerase small-molecule inhibitor (R1626) is also synergistic in combination with standard-of-care treatment. At AASLD, Roche reported interim phase 2a results showing that R1626 produced undetectable HCV RNA in up to 81% of participants. As drug resistance has been noted with certain polymerase inhibitors, investors anticipate that these new candidates could likely prove useful in combination therapies.

Combination therapies are also being explored in the area of biologics. For example, future clinical studies are expected to evaluate Peregrine Pharmaceuticals' bavituximab as a combination therapy for HCV.

Topical administration routes

One area in which biotech companies appear more active than big pharma is in the quest for a topical vaginal microbicide to prevent HIV and herpes infections. The absence of

large pharmaceutical interest is often attributed to perceived profit limitations from third-world markets and a need for extensive late-stage clinical trials. Clinical trials for these indications often require large enrollment numbers and considerable time for completion. As a result, funding has come not only from the biotech industry, but also from academia and private foundations, including the Bill & Melinda Gates Foundation (Seattle). These efforts are inspired by the Rockefeller Foundation (New York) Microbicide Initiative estimates, suggesting that a successful microbicide could achieve a global market of \$0.9 billion by 2011.

Plagued by drug candidates with low clinical efficacy, microbicide development recently suffered some late-stage setbacks. In July, Polydex Pharmaceuticals (Toronto) announced that phase 3 clinical development of their adsorption inhibitor candidate, Ushercell (a high molecular weight cellulose sulfate gel compound), was halted when interim analysis showed the vaginal gel was ineffective at preventing HIV seroconversion. Previously in 2006, Family Health International (Research Triangle Park, NC, USA) and Cellegy Pharmaceuticals (S. San Francisco, CA, USA) announced termination of phase 3 clinical trials evaluating another late clinical stage surfactant microbicide candidate—Savvy (glyminox; 1% C31G (a mixture of synthetic betaines and amine oxides with chain lengths varying from C(8) to C(20) with or without substituted groups) and equimolar concentrations of 16-carbon alkyl *N*-betaine and 14-carbon alkyl *N,N*-dimethylamine oxide)—which failed to show efficacy in the prevention of HIV infection.

Investor attention is now focused on three candidates nearing late-stage efficacy evaluation. Carraguard (λ - and κ -carrageenan), a fusion inhibitor sponsored by the Population Council (New York), is currently in phase 3 evaluation. Final analysis is expected by the end of this month. A second candidate, small-molecule PRO 2000, also in phase 3, is a sulfonated polymer fusion inhibitor under development by Indevus Pharmaceuticals (Lexington, MA, USA) and the Microbicides Development Program. Elsewhere, phase 1 clinical evaluations have shown Starpharma's (Melbourne, Australia) VivaGel (polylysine dendrimer technology)—which acts by blocking cell fusion and viral entry—to be safe and well-tolerated. VivaGel has been shown to provide significant efficacy in non-human primates, and is expected to undergo late-stage human efficacy testing next year.

Conclusions

The FDA approval this year of two first-in-class antivirals—Pfizer's (New York) Selzentry (maraviroc; Celsentri in the rest of the world) and Merck's (Whitehouse Station, NJ, USA) raltegravir—has heightened interest in drugs that target key viral mechanisms in other diseases. As a result, investors are exploring whether drug candidates with similar mechanisms of action can invigorate other antiviral markets. Biotech companies are instrumental in this effort, advancing novel candidates for unmet medical needs.

Among the breadth of novel candidates in clinical development, investors are paying particular attention to RNAi and whether it will live up to expectations. The high-profile \$1.1 billion buyout of Sirna Therapeutics (San Francisco) by Merck in October 2006 was seen as further validation of the RNAi space by investors. Although divided over the potential success of RNAi, many investors have been positioning themselves to profit in the event of a clinical breakthrough and have significantly raised market caps in the space. Although RNAi has generated considerable excitement, several outstanding issues argue for caution: will the potential immunostimulatory effects of RNAs prove to be problematic; will non-specific interactions cause adverse effects; and will it be possible to optimize RNAi delivery for systemic therapy? With highly anticipated RNAi candidates currently in mid-stage clinical trials, investors and the industry will soon find out whether these compounds achieve efficacy in human disease.

In summary, then, the next few years will be an exciting time for antiviral drug development. Across the antiviral space, biotech companies are answering the call for novel drug candidates, particularly in challenging diseases like HCV. With losses forecast as blockbuster drugs come off patent, big pharma continues to watch the antiviral space for viable candidates to fill their pipelines. Driven by the substantial profits expected for successful antiviral drugs, investors will likely continue to view this space as offering lucrative potential over the coming years.

COMPETING INTERESTS STATEMENT

The author declares competing financial interests: details accompany the full-text HTML version of the paper at <http://www.nature.com/naturebiotechnology>

1. Anonymous. *The World Market for Anti-Infectives, Volume III. Antiviral Drugs* (Kalorama Information, Rockville, MD, USA, 2007).
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