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HCV versus HIV drug discovery: Déjà vu all over again?

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ABSTRACT

Efforts to address HIV infection have been highly successful, enabling chronic suppression of viral replication with once-daily regimens. More recent research into HCV therapeutics have also resulted in very promising clinical candidates. This Digest explores similarities and differences in the two fields and compares the chronology of drug discovery relative to the availability of enabling tools, and concludes that safe and convenient, once-daily regimens are likely to reach approval much more rapidly for HCV than was the case for HIV.

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The discovery of drugs for the effective treatment of human immunodeficiency virus (HIV) infection has been a prominent area of success for the pharmaceutical industry, with dramatic benefits for human health worldwide. Twenty-seven small molecules have been approved since research in the area began in the 1980s.[1] At the same time, much progress has been made in the general optimization of molecular properties for convenient oral regimens. More recently, the race has been on to find small molecules to address chronic infection with hepatitis C virus (HCV). Great progress has been made: treatment paradigms are being revolutionized with the advent of direct-acting antivirals. This article was born out of a desire to explore to what extent medicinal chemistry as applied in the discovery of HCV has benefitted from earlier experiences with HIV.

Basis of comparison. In order to compare the histories of drug discovery for HIV and HCV, we chose to track the chronology of major events along with the availability of enabling research tools. Screening for suppression of viral replication in cells was a fundamental assay for lead optimization which for HCV came (in the form of the sub-genomic replicon)[2] a full 10 years after the discovery of the virus, delaying the development of the field considerably. We therefore also compared the chronologies relative to the availability of this tool. For some classes, the year of entry into clinical development is estimated. For both HIV and HCV, effective suppression of the virus in patients requires combination therapy for maximal compliance, and for this reason we have concentrated our analysis on oral agents. For HCV, we project probable approval dates based upon current Phase 3 trials. While different strains of the viruses cause significant morbidity in different geographic regions, we compare here the results of the main focus of discovery efforts thus far: HIV-1 for HIV and genotype 1 for HCV.

Historical context and prevalence. HIV was discovered in 1983, as the result of an urgent hunt to account for a cluster of deaths from rare opportunistic infections in the male gay community that became known as Acquired Immune Deficiency Syndrome (AIDS).[3] By the middle of that decade, it had become clear that the virus had already spread throughout most of the world, justifying the term 'pandemic'. Since then the prevalence of HIV infection worldwide has continued to rise, and the number of people living with the disease has also increased inexorably from approximately 10 M in 1990 to an estimated 34 M in 2010.[4] The

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latter rise is the result not only of new infections but also reduced mortality due to the expansion of access to antiretroviral therapy. In the US and Europe the impact of HIV drugs is especially apparent: although the number of AIDS-related deaths has varied little since 2000, there has been a 34% increase (to ca. 2.2 M) in the number of people living with HIV.

The high societal awareness of the disease and an unprecedented level of political advocacy stimulated vigorous research into therapies for HIV in both the public sector and the pharmaceutical industry, and the high level of mortality in the patient population justified the rapid clinical advancement of exploratory agents despite sub-optimal side effect profiles and treatment regimens. The complications of viral resistance soon became apparent, and the introduction in 1996 of combinations of three or more agents (highly-active antiretroviral therapy; HAART), enabling suppression of viral replication over many years, represented a major milestone, with mortality, diagnoses of AIDS, and hospitalizations all falling by 60–80% in the following 3 years.[5] Since then, ever more effective and convenient drug combinations and dosing regimens have been developed, with the impact of a once daily single tablet regimen (STR) in 2006 particularly evident.[6–8]

Like HIV, it became apparent after the discovery of HCV in 1989[9] that the virus was widespread: a staggering 3% of the world population has been estimated to be infected.[10] Immediate public awareness of the disease was much less than for HIV, but the long latency of chronic infection and the huge numbers involved have generated a substantial public health threat. Infection with HCV has become the leading cause of liver transplantation in the US;[11] a marked increase in HCV-related hepatocellular carcinoma is evident,[12] and mortality due to the sequellae of chronic HCV infection overtook HIV in 2007.[13]

Infection through blood transfusions prior to routine screening for HCV contributed to the widespread prevalence for the virus. Currently, both HIV and HCV are transmitted predominantly through the sharing of contaminated needles by intravenous drug users or through unprotected sex, particularly where there is a risk of compromising the mucosal barrier.[14]

HIV and HCV viral replication cycles and the clinical consequences of chronic infection. HIV is a retrovirus, transmitted as single-stranded, positive-sense RNA. Following entry into T lymphocytes, the viral RNA genome is reverse-transcribed into double-stranded DNA by the enzyme reverse transcriptase. The viral DNA is then transported to the nucleus and permanently inserted into the host genome through the action of viral integrase. Subsequent viral genome expression generates new viral RNA and proteins that are packaged for release from the cell and viral propagation. However, a prolonged period of latency (lasting many years in memory T cells) occurs in patients with therapeutically suppressed virus replication, making it impossible with current approaches to achieve total viral eradication in patients and mandating life-long therapy to prevent disease progression. Suppression of viral replication without pharmacological intervention is extremely rare, with the few known 'elite controllers' being the subject of intense scientific interest. The normal (untreated) consequence of acute infection with HIV is a 5–7 year period of clinical latency, followed by a gradual rise in viral load in plasma, a reduction in $CD4^+$ T lymphocyte count, constitutional symptoms and opportunistic diseases, resulting in death, usually within a decade after the primary infection.[15]

Following the cloning of HCV, elucidation of its biology was rapid and undoubtedly benefitted from prior experience with HIV. HCV is also transmitted as single-stranded, positive-sense RNA; RNA replication takes place in the cytoplasm of host liver cells via an assembly of viral and host proteins known as the replicase complex. With no integration into the host genome, complete eradication of the virus is possible. Unlike HIV, where the effective host immune response is specifically disabled by the virus, acute infection with HCV does not always lead to long-term disease: approximately 20% of individuals escape chronic infection. When chronic infection is established, further disease progression is slower than for HIV and highly variable, with ca. 10–15% individuals progressing to cirrhosis (and beyond, into hepatocellular carcinoma and end-stage liver disease) over the following 20 years.[16]

It is estimated that the average HIV-1 generation time (the time from release of a virion until a new viral particles are released from a subsequently-infected cell) is 2.6 days, and that total virion production in the average patient is 1×10^{10} daily.[17] Typically 10^3–10^6 virions/ml are found in plasma, with concentrations in lymph nodes 2–3 orders of magnitude higher. For HCV, total virion production per day is estimated to be even higher (ca. 10^{12}), with 10^6–10^7 infectious units of RNA/ml plasma.[18]

In general, RNA viruses exhibit a much higher replication error rate than their DNA counterparts, and this is evident for both HIV and HCV: while HIV generates approximately 3×10^{-5} errors per base per replication cycle,[19] HCV generates even more (about 1×10^{-4}/cycle).[20] The higher viral load and error rate for HCV over HIV allows the former to sample genetic space more efficiently, with a swarm of quasispecies (of varying fitness) populating individual patients, and in general resistance emerges more rapidly with monotherapy in HCV than HIV. HCV genetic diversity is also much broader than that of HIV, and as a consequence targets for HCV therapy are less conserved; whilst most HIV drugs are active against all subgroups and clades of HIV-1 (and often also HIV-2 and SIV), an on-going challenge for HCV is to find agents outside the nucleoside class that retain activity across all genotypes.

Comparisons by mechanistic class. Inhibitors of the viral polymerases and proteases are prominent in the clinical armamentarium for both viruses, and are compared by class below. Agents with clinical utility acting via other mechanisms unique to the virus (integrase and CCR5 for HIV, NS5A for HCV) are then discussed as a group.

Nucleoside and nucleotide polymerase inhibitors. These drugs, regarded as the backbone of therapy in HIV and highly valued in HCV due to their high barrier to resistance, inhibit viral replication through incorporation into the nascent viral nucleic acid and subsequent chain termination. As such, the bioactive entities are nucleoside triphosphate analogs that compete with the natural nucleotide pools within infected cells as substrates for the viral polymerase. To generate these, nucleoside inhibitors must undergo three kinase-mediated intracellular phosphorylation steps, whereas nucleotide inhibitors bypass the first step by delivering a monophosphate analog directly into the cell. As might be expected, the medicinal chemistry of these agents is dominated by the twin challenges of selectivity for viral over host polymerases (affecting therapeutic index) and by the effective delivery and half-life of the bioactive species in the target tissue (affecting dose and regimen, respectively).

The first antiretroviral agent to be studied clinically for the treatment of HIV was Zidovudine (AZT; Fig. 1). The molecule existed[21] before the virus was discovered, and its activity was revealed in early screening efforts; it advanced very rapidly into and through clinical trials, receiving regulatory approval (after only 3 years) in 1987. A further five nucleosides followed, including the once-daily abacavir, before the only nucleotide, tenofovir dipivoxil, was approved 14 years later. The most recent nucleoside to be approved was Emtricitabine (FTC), in 2003.

Analogs of each of the natural bases are represented in the family of approved antiretroviral nucleos(t)ides. The ribose sugar can be replaced by unsaturated, thioacetal and even acyclic alternatives, illustrating the tolerance of reverse transcriptase for substrate diversity, but all the agents lack a 3′-OH substituent, ensuring chain termination following incorporation. The nucleo-

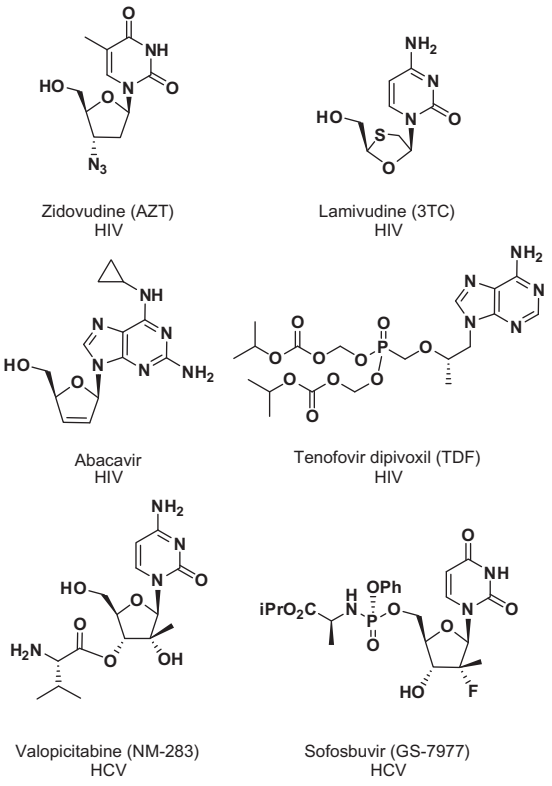


Figure 1. Examples of nucleos(t)ide analogs.

sides are all administered as the parent drug, but the phosphonic acid derivative tenofovir lacks oral bioavailability. In this case efficient loading of lymphatic cells is achieved through oral administration of the bis-methyleneoxycarbonate ester (which, interestingly, is not observed in plasma).[22]

The discovery of nucleosides for the treatment of HCV benefitted from exploratory work with bovine viral diarrhea virus as a surrogate system prior to the availability of the replicon assay. Despite intensive efforts, the generation of clinically-useful agents has taken far longer than for HIV. Ironically, the prototypical HCV chain terminator 2′-C-Me-A (in which elongation is prevented for steric reasons), like AZT, existed before the virus was discovered,[23] but finding an acceptable balance between facility for intracellular phosphorylation, rate of incorporation, selectivity over host polymerases (i.e., safety), and oral bioavailability has proved a formidable challenge. Furthermore, the stringency of the structural requirements for chain incorporation for HCV is such that it has proven impossible to identify nucleoside phosphonates, analogous to those developed for HIV, with useful levels of activity.

Valopicitabine[24] was the first agent to demonstrate the potential value of the class, entering clinical trials 5 years after the availability of the replicon assay (15 years after the discovery of the virus). Oral bioavailability was achieved through active transport of the valine prodrug of the nucleoside. Clinical attrition of this and subsequent candidates has been high. The most promising agent in the class is sofosbuvir, which is currently in Phase 3; in this case the first kinase step is by-passed by direct delivery of the monophosphate into hepatocytes through the use of a phosphoramidate prodrug. The long intracellular half-life of the triphosphate enables once-daily dosing.[25]

Non-nucleoside polymerase inhibitors (*NNIs*). Many allosteric inhibitors of HIV reverse transcriptase and HCV NS5B have been discovered, all through high-throughput screening (HTS). For reverse transcriptase, there is a single site to which diverse structures bind that is somewhat plastic and largely hydrophobic in nature, with no ionic interactions. Thus while it proved easy to achieve good levels of activity in vitro, incorporating sufficient metabolic stability and solubility for clinical utility was more difficult. Nevirapine[26] (Fig. 2) was the first HIV non-nucleoside reverse transcriptase inhibitor (NNRTI) to be approved, in 1996 (12 years after the availability of the cell-based assay). Four other NNRTIs have followed, with the most recent, rilpivirine,[27] approved in 2011.

In contrast to reverse transcriptase, at least four distinct allosteric sites have been identified on NS5B by which the enzyme can be inhibited. The optimization of HTS hits for all of these sites was facilitated by protein crystallography, with the structure of NS5B[28] becoming available at about the same time as the replicon assay. The first HCV clinical candidate came from pioneering work at Japan Tobacco[29] and entered the clinic only 2 years after the replicon became available, but it and many other agents since have failed to progress beyond initial studies. More recently the situation has improved, and Figure 2 displays the structures of the most advanced agents to date; all are in Phase 2b clinical trials. BMS-791325[30] binds at Thumb Site 1, lomibuvir[31,32] at Thumb Site II,

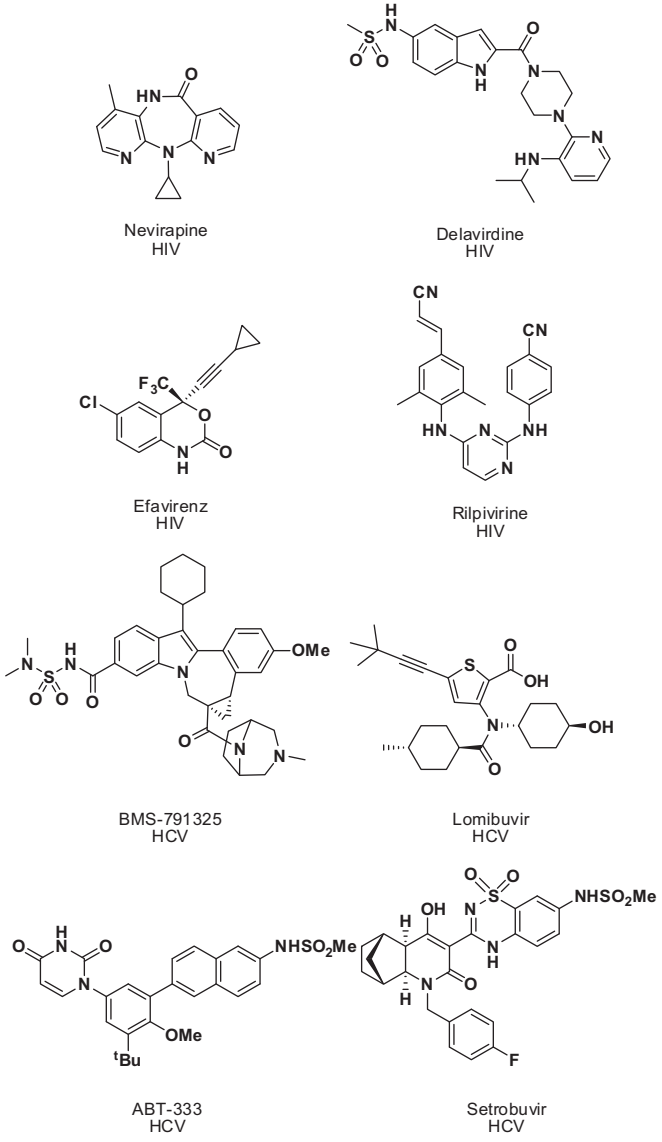


Figure 2. Examples of non-nucleoside inhibitors.

and ABT-333[33] and setrobuvir[34] at Palm Site 1. All these agents derive much of their potency from hydrophobic interactions, but three of the four also contain an acidic residue that is critical for activity. These compounds are therefore the result of careful modulation of plasma protein binding and minimization of both Phase 1 and Phase 2 metabolism; despite this, the low volume of distribution inherent to lipophilic acids makes it difficult to achieve a once-daily profile.

Protease inhibitors. The proteases of both HIV and HCV have been the targets of intensive research efforts ever since their identification, and in both cases rational design approaches based upon knowledge of the substrate and the catalytic mechanism have been the most successful. HIV is an aspartyl protease that has become particularly well known for crystallographic studies, but it was the similarity to another aspartyl protease, renin, which provided the initial impetus for lead discovery; the first HIV protease inhibitor to enter the clinic, saquinavir (Fig. 3),[35] did so in approximately a year after the protein crystal structure was solved.[36] The structural hallmark of the series is the secondary alcohol that mimics the hydrated amide of the transition state.

Saquinavir received regulatory approval in 1995, 11 years after cell-based assays became available, and nine other agents followed over the next decade. Just as for the peptide-based renin inhibitors, achieving satisfactory plasma levels following oral administration was non-trivial, but the field was transformed by the finding that ritonavir, the second agent to be approved, irreversibly inhibits CYP 3A4 during the course of its metabolism.[37] The dose required for complete inhibition of CYP 3A4 is only 1/6 of the therapeutic dose for inhibition of viral replication, and ritonavir is co-administered at this lower dose with six of the eight subsequent agents to boost their pharmacokinetics. Unfortunately, ritonavir is administered in soft-gel capsules, adding to the pill burden for patients. Atazanavir (boosted with ritonavir) has achieved widespread use within the class due to its reduced potential for lipidogenesis and its once-daily profile.[38]

The fundamental and general medicinal principle that free (unbound) drug is the species that drives efficacy emerged partly through lessons learned in the clinical evaluation of HIV protease inhibitors,[39] and a unique feature of the class is that, while resistance to the first generation of PIs is readily generated in vitro, second generation PIs such as darunavir require multiple mutations in the active site of the enzyme to generate resistant viral progeny whose replicative fitness is often substantially attenuated. Breakthrough of PI-resistant mutants clinically is rarely seen: the time within the dosing interval that free drug levels are sufficient to inhibit the wild-type but not mutant virus is relatively short.[40]

In contrast with HIV, HCV NS3 is a serine protease, and two distinct strategies for inhibitor design have been pursued. The first to succeed was the covalent-reversible ketoamide class, with boceprevir[41] and telaprevir[42] (Fig. 3) receiving approval on successive days in May 2011. However, the first entrant into clinical trials was the product-like carboxylic acid BILN-2061, the result of extraordinarily innovative work at Boehringer Ingelheim.[43] Here dramatic potency enhancement was achieved through incorporation of a large quinoline-based moiety extending beyond the P2 position and lying over the relatively flat surface of the protein. Further medicinal innovation is evident in the proactive use of new synthetic methodology (olefin metathesis) to incorporate a macrocycle to reinforce the bioactive conformation.

Competition in the product-based inhibitor series has been intense, and three candidates have reached Phase 3 trials, with asunaprevir[44] being studied in an all-oral regimen (with daclatasvir, see below) in GT 1b patients.

PK–PD relationships of HCV protease inhibitors are interesting in that, in several cases, active transport into hepatocytes appears

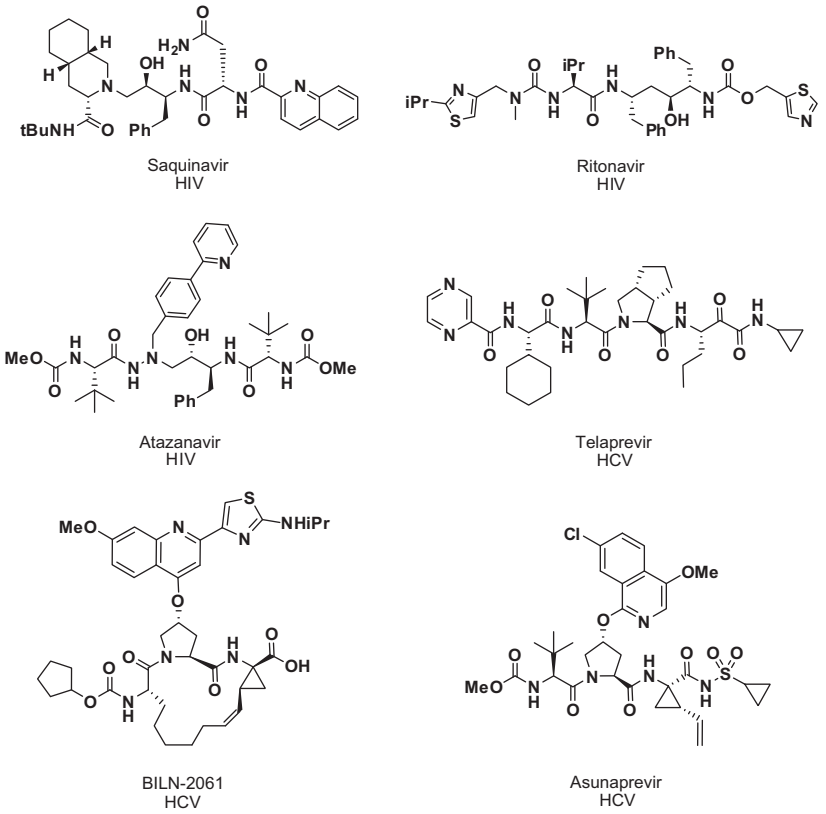


Figure 3. Examples of protease inhibitors.

to generate free drug levels in the target tissue that are higher than those in plasma, leading to greater efficacy than would be predicted by plasma exposure.[45]

In an era in which medicinal chemists have become far more aware of molecular properties that are typical for oral drugs and that avoid toxicological liabilities,[46] NS3 protease inhibitors are notable for the extent to which they transgress the Lipinski guidelines. This serves as a reminder that useful oral drugs can still be found even when the target binding site mandates large molecules with many H-bond donor and acceptor atoms to confer sufficient inhibitory potency.[47]

Agents acting via other mechanisms. Integration into the host chromosome is an essential step in the replication cycle of HIV. This complex process involves endo-cleavage of a dinucleotide from the 3′ end of the proviral DNA ('3′-processing') followed by nucleophilic attack of the newly-liberated 3′-OH groups on the phosphodiester backbone of the host DNA (strand transfer), both steps of which are catalyzed by the viral integrase. As with many enzymes manipulating phosphate esters, Mg^{2+} is an essential cofactor for integrase, and early HTS (based upon 3′-processing assays) identified both small molecule and natural product-derived β-ketocarboxylates as hits. Despite optimization to excellent levels of potency in enzyme assays, none of these series demonstrated antiviral activity, and it was not until the advent of a strand transfer assay approximately a decade after the discovery of the virus that the situation was remedied.[48] Pharmacokinetic optimization then presented a further significant challenge, with excellent metabolic stability required to mitigate low volumes of distribution and yield an acceptable half life in vivo. Consequently it took approximately 20 years from the availability of an antiviral assay for the first candidate, raltegravir,[49] to enter the clinic, and approval (with a twice-daily regimen) followed in 2007. The second agent, elvitegravir,[50] was approved in 2012, and in this case a very direct benefit was derived from innovation in HIV protease inhibitors: the once-daily regimen is achieved through pharmacokinetic enhancement with cobicistat (Fig. 4), which is an irreversible inhibitor of CYP3A4, designed from ritonavir, completely *lacking* HIV protease activity—thereby avoiding any risk of protease resistance development in a protease-free regimen.[51]

Another product of a long discovery history is maraviroc, which antagonizes the interaction of HIV with the host surface receptor CCR5. In this case, once the biological details of entry had been established,[52] lead optimization of lipophilic amines found by HTS required careful modulation of both log*P* and pK_a, as well as minimization of metabolism, to avoid hERG channel interactions and CYP inhibition.[53] As a result, the rate of advancement into and through clinical trials was similar to that of the integrase inhibitors. Specific details for the mechanism of entry of HCV into hepatocytes, by contrast, remain relatively poorly defined.

The discovery of daclatasvir was a tour-de-force of meticulous phenotype screening, completely dependent upon the availability of the HCV replicon assay.[54] Following HTS, the initial relatively weak activity of a hit was found not to be associated with the structure of the principal molecular component in the screening well. Bioassay-guided fractionation of the minor components of the mixture identified a dimeric byproduct with picomolar activity that provided the starting point from which daclatasvir was optimized. While it has been established that NS5A is essential for viral replication, its function remains unknown, and the locus of action of daclatasvir was identified as being on NS5A by resistance studies. Initial clinical results with daclatasvir, announced in late 2008,[55] were startlingly positive (3.3 $\log_{10}$ reduction in viral RNA in plasma following a single 100 mg dose) and stimulated immediate and intense competition. Daclatasvir has reached Phase 3, and already several related compounds are also in advanced clinical development. Like the NS3 protease inhibitors, these compounds

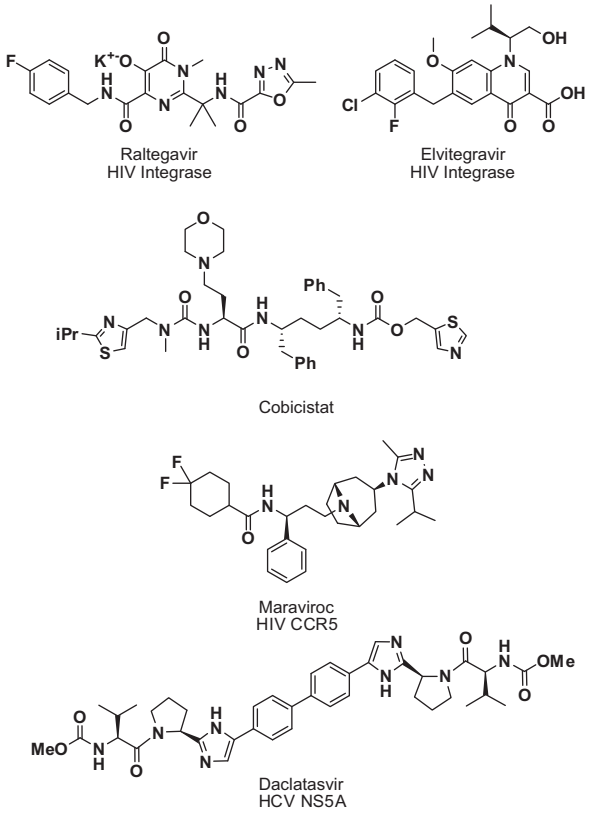


Figure 4. Integrase inhibitors, NS5A inhibitors and cobicistat.

are all striking for their non-compliance with conventional structural guidelines for orally effective drugs.

Clinical combinations of antivirals and single-tablet regimens. The advent of HAART, while representing a major medical advance in the ability to suppress HIV replication over many years, presented a real problem for patients. Initial antiviral combinations involved diverse and complex regimens involving 20–30 tablets and/or capsules daily,[56] with differing dosing frequency and limitations relative to mealtimes, diet and sleep. It has since been shown that resistance emerges when as few as one in 20 doses are missed,[57] making long-term compliance to maintain viral suppression practically impossible. Thus the ingenuity of the medicinal chemist in devising drugs with once-daily regimens was particularly important for maximal patient benefit—and further, the reduction in dose to enable the development of STRs was an important advance (no small task, given the doses that are typical of anti-infectives). In practice, HAART was introduced in 1996, but it took until 2006 for the first once daily STR (Atripla®; tenofovir dipivoxil 300 mg, emtricitabine 200 mg and efavirenz 600 mg) to be approved. A mark of how the field has evolved with regard to combination regimens is that two of the four components in the most recently-approved STR (elvitegravir and cobicistat in Stribild™) had not received prior approval as single agents.

From the clinical experience with HIV, it was apparent for HCV that combination therapy with antivirals was likely to be required for effective viral suppression. Ironically, the initial introduction of direct-acting antivirals has actually complicated therapy. Prior to the introduction of the first protease inhibitors, standard of care constituted administration of pegylated interferon and ribavirin for 48 weeks. Although the addition of a protease inhibitor to this regimen improves SVR rates from ~55% to ~75%, the treatment burden for the patient is substantially increased, with the side effects of telaprevir and boceprevir adding to the poorly-tolerated earlier agents. Furthermore, both compounds require administra-

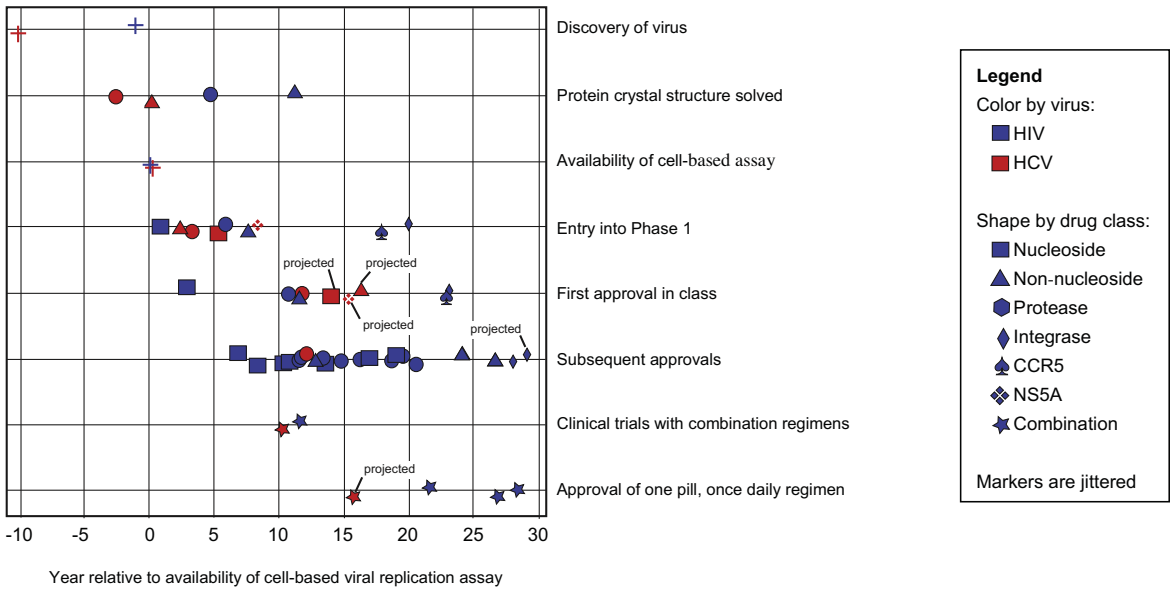


Figure 5. Comparative chronology of direct-acting antiviral drug discovery for HIV and HCV.

tion three times a day. Thus, interferon-free (and preferably ribavirin-free) regimens hold the prospect of a benefit to the patient analogous to HIV, with a once-daily single tablet regimen the ultimate goal. The pioneering study of a combination of non-approved drugs in an interferon-free regimen (the nucleoside prodrug mericitabine with the PI danoprevir in the INFORM-1 trial)[58] therefore represented a further important innovation in the field.

Chronological comparisons. In comparing the rates of drug discovery for HIV and HCV, two differences in clinical context must be borne in mind. The race to discover agents to treat HIV infection was driven by an urgent need for saving lives in the face of no alternatives. For HCV, the availability of interferon-based regimens, although of limited efficacy, mandated a more stringent safety profile for the first direct-acting antiviral agents. Another important difference is the logistics of late-stage clinical trials: whereas these are typically of 48 weeks duration for HIV, the time to SVR for HCV has been falling as the potency of the regimens has improved and trials of only 12 weeks duration are now common. The larger pool of HCV patients also facilitates enrollment.

It is evident from the normalized timeline in Figure 5 that the rate of clinical advancement of HIV nucleosides was extraordinarily rapid, with first approval almost a decade earlier than all other classes for either virus. The NNIs show the greatest difference in clinical timelines: although the first HCV NNI started Phase 1 very shortly after the replicon became available, the HIV NNRTI nevirapine reached approval at least four years faster than is likely to be the case for HCV. The first HCV protease inhibitor entered the clinic at about the same time relative to the availability of a cell-based assay as the first HIV protease inhibitor, and the speed to first approval (although for a different agent) was also similar. HCV NS5A inhibitors are the only other class whose speed of development matches nucleosides, NNIs and PIs—perhaps as a consequence of their phenotypic mode of discovery.

The impact of combination regimens in the treatment of HIV has had a profound influence upon HCV drug discovery. Not only did it stimulate multiple avenues of research in parallel to discover mechanistically complementary agents, but clinicians have been quick to adopt analogous combination strategies. This is evident from Figure 5 in that the initiation of clinical trials with combination agents for HCV predates first approval for any agent, whereas for HIV the introduction of HAART came over a decade after the approval of AZT.

Overall, it took 12 years for three classes of HIV agents to be available to patients (Nucs, NNIs, PIs), with the fourth and fifth classes (CCR5 antagonists and integrase inhibitors) following 11 years later. By contrast, projecting success from current Phase 3 candidates, four classes of HCV agents will be available in 16 years from the invention of the replicon (ca. 2015), and there are clear indications from Phase 2 studies that interferon-based regimens will soon become obsolete. Most dramatically, it seems reasonable to project that the first once daily STR for the treatment of HCV will become available at least 5 years faster than for Atripla®.

Conclusions. The AIDS virus was discovered in 1983, and it was not until 2006 that the pharmaceutical industry delivered the maximum benefit to patients in the form of a once-daily STR to enable chronic compliance. HCV was discovered 6 years after HIV, and the replicon assay became available a full 15 years after cell-based HIV replication assays. The mechanistic similarity between the viruses, the dramatic advances in molecular biology and biochemical science, as well as the general improvement in ability to optimize for and predict human pharmacokinetics in the intervening years, might lead one to hope that the time to delivery of similarly safe, efficacious and convenient regimens for HCV patients would be substantially shorter.

Two general recent advances in medicinal chemistry are indeed apparent when reflecting on HCV drug discovery efforts so far. Firstly, there has been widespread application of lessons of PK–PD previously established across all therapeutic areas, but particularly in infection, with the free drug principle pre-eminent. Secondly, new synthetic methodology continues to play a key enabling role: the NS3 protease field has been greatly influenced by the use of olefin metathesis to explore the benefit of macrocyclic structures, and this in turn has engendered similar exploratory efforts in other contexts.[59]

Despite these technological advances, the speed with which the first HCV agents entered the clinic was no faster than for HIV, and the time taken for boceprevir and telaprevir to reach approval was no faster relative to the first HIV drugs. Why is this? Apart from the special circumstances contributing to the urgency for HIV drugs described above, we contend that it remains a profoundly challenging exercise to identify molecules with the properties necessary for clinical utility, illustrating the need for long-term commitment to ensure success. It is notable that none of the com-

ponents of marketed STRs for HIV were first-in-class for their mode of action; rather, the paradigm was one of learning from the clinical shortcomings of early compounds to inform the design of subsequent drugs. The same paradigm is being applied in HCV, but in this case once-daily compounds suitable for convenient regimens are emerging considerably more rapidly.

The discovery of drugs for the effective treatment of chronic HIV infection has been a dramatic success for medicinal chemistry, and we are on the verge of realizing a second major achievement in addressing the challenge posed by HCV. Although the initial rates of discovery have not differed dramatically, there is every reason to expect from the diverse agents currently in late-stage clinical trials for HCV that the ultimate once-daily STR regimen will indeed become available much more rapidly than for HIV, transforming the lives of patients and, through reducing the morbidity associated with end-stage liver disease, providing a substantial benefit to society in general.

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