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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-

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