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Innovation and trends in the development and approval of antiviral medicines: 1987–2017 and beyond

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ABSTRACT

2017 marked the 30th anniversary of the approval of zidovudine (AZT) as the first HIV/AIDS therapy. Since then, more than eighty antiviral drugs have received FDA approval, half of which treat HIV infection. Here, we provide a retrospective analysis of approved antiviral drugs, including therapeutics against other major chronic infections such as hepatitis B and C, and herpes viruses, over the last thirty years. During this time, only a few drugs were approved to treat acute viral infections, mainly influenza. Analysis of these approved antiviral drugs based on molecular class and mode of action shows that a large majority are small molecules and direct-acting agents as opposed to proteins, peptides, or oligonucleotides and host-targeting therapies. In addition, approvals of combination therapies accelerated over the last five years. We also provide a prospective study of future potential antiviral therapies, based on current clinical research pipelines across the pharmaceutical industry. Comparing past drug approvals with current clinical candidates hints at the future evolution in antiviral therapies and reveals how antiviral medicines are often discovered. Overall, this work helps forecast future trends and innovation in the field of antiviral research and development.

1. Introduction

1.1. Scope of the study

The field of antiviral research has taken on a new dimension since the global spread of human immunodeficiency virus (HIV) caused the acquired immune deficiency syndrome (AIDS) epidemic in the 1980s, with unprecedented efforts in academic and pharmaceutical laboratories to develop new effective antiviral therapies. These efforts have led to advances in basic science and many therapeutic breakthroughs including development of inhibitors targeting HIV and other viruses. In this review, we analyze all antiviral therapeutics on the market since the approval of zidovudine (Retrovir®) on the basis of clinical indication, molecular size (small versus large), mode of action (or molecular target), and use in combination with other therapeutic agents. We also report all antiviral therapeutics currently in clinical-stage evaluation with the goal of comparing current research with past approvals to predict potential trends and changes in antiviral medicine. This work also helps to understand the driving forces behind innovation and success in antiviral research.

1.2. Definitions and method of analysis

1.2.1. FDA-approved drugs

The information about antiviral drugs for this evaluation was gathered directly from the Food and Drug Administration (FDA) Drug Database (https://www.accessdata.fda.gov/scripts/cder/daf/). Monthly approval reports from January 1987 through December 2017 were scanned to create an exhaustive list of 179 antiviral medications approved in the United States over the 30-year period. To narrow the focus to novel therapeutic agents, the list was condensed further by restricting it to drugs submitted as either Class 1 (new molecular entity [NME]) or Class 4 (new combination) to eliminate approvals related to formulation changes, such as extended-release versions of previously approved drugs (https://www.fda.gov/downloads/aboutfda/centersoffices/)
Out of 88 approved antiviral drugs, ten were discontinued or withdrawn (marked as a in Table 1).

1.2.2. Drugs in development

Four criteria were established to include drug candidates on the list of antivirals in development for this evaluation. Each drug candidate was required to be: (1) in human trials, Phase 1–3, (2) a therapeutic agent (i.e., not a vaccine), (3) submitted to the US FDA or listed in ClinicalTrials.gov, and (4) in “active” development, meaning a clinical or company update was evident in the past 2 years. The initial list of drug candidates in clinical development was gleaned from research pipeline information available on company websites (both large and small companies active in the antiviral drug development space). Next, recent published reviews covering drug development for different viruses or drug classes were screened, e.g. (Salazar et al., 2017). Finally, the list was supplemented by records generated through Informa’s PharmaProjects database.

1.3. Trends for 1987–2017

The chronological order of market approvals for antiviral drugs over the last thirty years is represented in Fig. 1. The cumulative analysis of FDA-approved antivirals during this time interval shows an almost linear progression of about 2.8 approvals per year (Fig. 2A). This represents roughly one-tenth of the yearly FDA approvals across all indications (https://www.fda.gov/downloads/aboutfda/transparency/basics/ucm247465.pdf). A more detailed inspection of the number of antiviral agent approvals per year reveals two discrete waves, the first corresponding to the emergence of HIV therapeutics (Fig. 2B). The indication with the single largest share of antiviral agent approvals during the 1997–2006 period (Fig. 3A) and include five unique interferons, one monoclonal antibody, one peptide, and one oligonucleotide. The first large molecule approved for antiviral therapy was interferon alpha-2b (Intron A®), a mixture of human interferon alpha proteins used to treat external genital warts associated with HPV since 1988 (Suppl 1). Different forms of recombinant interferons were subsequently approved, such as interferon alpha n3 (Alferon N®) in 1998 also treating HPV-associated infection, with interferon alfacon-1 (Infergen®) being the first HCV therapeutic in 1997. Pegylated interferons were then introduced soon after the approvals of peginterferon Alfa-2B (Pegintron/Sylatron®) in 2001, and peginterferon Alfa-2A (Pegasys®) in 2002. The only antiviral monoclonal antibody, palivizumab (Synagis®), was approved in 1998 for the prophylactic treatment of infants at risk of contracting severe RSV infection. In 2003, the 36 amino acid peptide enfuvirtide (Fuzeon®) received FDA approval for the treatment of HIV-1 infection in salvage therapy. The only approved antiviral oligonucleotide, fimoviren (Vitravene®), is an antisense antiviral drug used to treat cytomegalovirus (CMV)-induced retinitis in immunocompromised patients.

1.4. General attributes of approved antiviral drugs

1.4.1. Indications

With 43 approvals during the 1987–2017 period, HIV-1 is the indication with the single largest share of antiviral agent approvals (Fig. 2C). The indication with the next largest share of approvals is HCV, with 17 during the same interval. When combined, HIV-1 and HCV therapeutics account for more than two-thirds of all antiviral drug approvals from 1987 to 2017 (Fig. 2B and C). Eleven and eight drugs have been approved to treat Herpesvirusiae (cytomegalovirus [CMV] and herpes simplex virus [HSV]) and HBV infection, respectively. Finally, four drugs were approved to treat external genital warts associated with human papilloma virus (HPV) infection. Taken together, drugs approved to treat chronic viral infections represent over 90% of all antivirals approved during the last 30 years. With respect to acute infections, five drugs were approved to treat respiratory viruses: four for the treatment of influenza infection, and one for respiratory syncytial virus (RSV).

1.4.2. Small versus large molecules

Small molecules represent the dominant class of antivirals, with 77 approvals out of the total of 88. Most antiviral large molecules were approved during the 1997–2006 period (Fig. 3A) and include five unique interferons, one monoclonal antibody, one peptide, and one oligonucleotide. The first large molecule approved for antiviral therapy was interferon alpha-2b (Intron A®), a mixture of human interferon alpha proteins used to treat external genital warts associated with HPV since 1988 (Suppl 1). Different forms of recombinant interferons were subsequently approved, such as interferon alpha n3 (Alferon N®) in 1989 also treating HPV-associated infection, with interferon alfacon-1 (Infergen®) being the first HCV therapeutic in 1997. Pegylated interferons were then introduced soon after the approvals of peginterferon Alfa-2B (Pegintron/Sylatron®) in 2001, and peginterferon Alfa-2A (Pegasys®) in 2002. The only antiviral monoclonal antibody, palivizumab (Synagis®), was approved in 1998 for the prophylactic treatment of infants at risk of contracting severe RSV infection. In 2003, the 36 amino acid peptide enfuvirtide (Fuzeon®) received FDA approval for the treatment of HIV-1 infection in salvage therapy. The only approved antiviral oligonucleotide, fimoviren (Vitravene®), is an antisense antiviral drug used to treat cytomegalovirus (CMV)-induced retinitis in immunocompromised patients.

1.4.2.1. Mono- and combination therapies

Although combination therapies are now widely used for antimicrobial and anticancer treatments, the concept of combination therapy was originally pioneered for antiretroviral treatments. The main purpose of combination therapies is to prevent or delay the emergence of drug resistance by inhibiting viral replication at multiple points in the viral life cycle. During the 1987–2017 period, antiviral monotherapy approvals totaled 64 and combination therapy approvals totaled 24 (Fig. 3B). Approval of the initial combination therapies against HIV-1 infection followed the approvals of the individual components as monotherapies, which helps explain their later emergence as combination drug therapy approvals (Fig. 3B). Lamivudine/zidovudine (Combivir®) was the first fixed-dose combination therapy approved for HIV-infected patients in 1997, soon after the approval of lamivudine in 1995 (Fig. 1). For HCV combination therapies, most NMEs were approved as part of a combination therapy without any prior individual drug approval. One notable exception is sofosbuvir (Sovaldi®), which was approved first in 2013 as a monotherapy against HCV and was approved soon after in combination therapies: Harvoni® in 2015, Epclusa® in 2016, and Vosevi® in 2017 (Fig. 1 and Table 1).

1.4.3. Virus- versus host-targeting agents

Over the last thirty years, only thirteen antiviral drug approvals (ten NMEs) target host mechanisms; most approved antivirals work as virus-targeting (or direct-acting) agents interacting with viral targets (Fig. 4A). Approved host-targeting molecules include interferons as immunomodulating agents (interferon alpha-2b, interferon alpha-n3, interferon alfacon-1, peginterferon Alfa-2b, and peginterferon Alfa-2A). Five host-targeting small molecules have been approved. Imiquimod (Aldara®) is a toll-like receptor (TLR7) agonist approved in 1997 for the topical treatment of genital and perianal warts, superficial basal cell carcinoma, and actinic keratosis. Docosanol (Abreva®) was approved as a topical cream in 2000 to treat herpes labialis caused by HSV-1 infections. Although the mechanism of action of docosanol is not entirely understood, its very broad antiviral spectrum and interaction with plasma membranes suggests that it does not act directly on viral particles (Leung and Sacks, 2004). In 1998, ribavirin (Rebetol®), a guanosine analog, was approved for the treatment of HCV infection.
| Year | Trade Name | Generic Name (Abbreviation) | Indication (Virus) | Target (MOA) | Type | Mono/Combo |
|------|------------|-----------------------------|-------------------|-------------|------|-----------|
| 1987 | Retrovir  | Zidovudine (AZT)            | HIV-1             | Pol         | Small Molecule | Mono |
| 1988 | Intron A  | Interferon Alfa-2B (INT2B)  | HPV               | Host        | Protein     | Mono |
| 1989 | Cytovene  | Ganciclovir Sodium (GAN)    | CMV               | Pol         | Small Molecule | Mono |
| 1989 | Alferon N Injection | Interferon Alfa-N3 (INTN3) | HPV               | Host        | Protein     | Mono |
| 1991 | Intron A  | Interferon Alfa-2B (INT2B)  | HCV               | Host        | Protein     | Mono |
| 1991 | Foscarnet | Foscarnet Sodium (FOS)      | CMV               | Pol         | Small Molecule | Mono |
| 1991 | Videx®   | Didanosine (ddI)            | HIV-1             | Pol         | Small Molecule | Mono |
| 1992 | Hivid®    | Zalcitabine (ddC)           | HIV-1             | Pol         | Small Molecule | Mono |
| 1992 | Intron A  | Interferon Alfa-2B (INT2B)  | HBV               | Host        | Protein     | Mono |
| 1993 | Flumadine | Rimantadine (RIM)           | Influenza         | O           | Small Molecule | Mono |
| 1994 | Zerit     | Stavudine (d4T)             | HIV-1             | Pol         | Small Molecule | Mono |
| 1994 | Famvir®   | Famciclovir (FAM)           | HSV               | Pol         | Small Molecule | Mono |
| 1995 | Valtrex  | Valacyclovir Hydrochloride (VAL) | HSV               | Pol         | Small Molecule | Mono |
| 1995 | Epivir    | Lamivudine (3TC)            | HIV-1             | Pol         | Small Molecule | Mono |
| 1995 | Inivirase | Saquinavir Mesylate (SQV)   | HIV-1             | Pr          | Small Molecule | Mono |
| 1996 | Norvir    | Ritonavir (RTV)             | HIV-1             | Pr          | Small Molecule | Mono |
| 1996 | Crixivan  | Indinavir Sulfate (IDV)     | HIV-1             | Pr          | Small Molecule | Mono |
| 1996 | Viramune  | Nevirapine (NVP)            | HIV-1             | Pol         | Small Molecule | Mono |
| 1996 | Vistide®  | Cidofovir (CID)             | CMV               | Pol         | Small Molecule | Mono |
| 1996 | Denavir   | Penciclovir (PEN)           | HSV               | Pol         | Small Molecule | Mono |
| 1997 | Aldara    | Imiquimod (IMI)             | HPV               | Host        | Small Molecule | Mono |
| 1997 | Viracept® | Nelfinavir Mesylate (PFV)   | HIV-1             | Pr          | Small Molecule | Mono |
| 1997 | Rescriptor| Delavirdine Mesylate (DLV)  | HIV-1             | Pol         | Small Molecule | Mono |
| 1997 | Combivir | Lamivudine (3TC)/Zidovudine (AZT) | HIV-1 | Pol/Po | Small Molecule Combo |
| 1997 | Interferon Alfacon-1 (INTA1) | HIV-1 | Pol | Small Molecule | Mono |
| 1997 | Synagis  | Palivizumab (PAV)           | RSV               | O           | Protein     | Mono |
| 1998 | 1998   | Rapivab | Peramivir (PER) | Influenza | O | Small Molecule | Mono |
| 2014 | Harvoni | Ledipasvir (LED)/Sofosbuvir (SOF) | HCV NS5A/Pol | Small Molecule Combo |
| 2014 | Vitekta | Elvitegravir (EVG) | HIV-1 | Int | Small Molecule | Mono |
| 2014 | Harvoni | Ledipasvir (LED)/Sofosbuvir (SOF) | HCV NS5A/Pol | Small Molecule Combo |
| 2014 | Rapiya | Peramivir (PER) | HIV-1 | Int | Small Molecule | Mono |

(continued on next page)
Ribavirin is believed to have multiple mechanisms of action, including immunomodulation and inhibition of human inosine-5′-monophosphate dehydrogenase (IMPDH) (Paeshuysse et al., 2011). In 2007, maraviroc (Selzentry®) was approved to treat HIV-1 infection by targeting C-C chemokine receptor type 5 (CCR5), one of the main host chemokine receptors for virus entry into T-cells. Topical Sinecatechins (Veregen®) is a water extract of green tea leaves that was approved in 2006 for treatment of genital warts caused by the HPV, without a well-defined mechanism of action.

1.5. Mechanisms of action of direct acting agents

Out of the 88 therapies approved between 1987 and 2017, 72 were unique NMEs. Each NME was classified as targeting either the viral Viruses.
HIV-1 = Human immunodeficiency virus-1.
HCV = Hepatitis C virus.
HBV = Hepatitis B virus.
CMV = Cytomegalovirus.
HSV = Herpes simplex virus.
HPV = Human papillomavirus.

Targets.
Pol = Polymerase.
Pr = Protease.
Int = Integrase.
NS5A = Nonstructural protein 5A.
O = Other.
Other abbreviations.
Mono = Monotherapy.
Combo = Combination therapy.
* Discontinued or Withdrawn.

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categories: nucleoside analogs and non-nucleoside inhibitors. Although other classi-
timetabolites such as acyclovir (Zovirax®) for HIV-1 treatment, other nucleoside analogs used as virus-targeting an-
sense oligonucleotide and oseltamivir (Tamiflu®) for influenza virus-targeting agents (Fig. 4B). Polymerase inhibitors fall into two 
host-targeting agents approved between 1987 and 2017 (Fig. 4B). With 
main protein targets of antiviral agents. Inhibitors of viral enzymes 
cognized and phosphorylated by host nucleo(s/t)ide kinases. Long-term 
synthesis of viral nucleic acid. This means that nucleoside analogs must 
cleosides and are used, in their triphosphate forms, as substrates for the 
approved. Nucleoside analogs are prodrugs that mimic natural nu-

classified include fomivirsen (Vitravene®) for HSV and acyclovir (Zovirax®), which is an anti-
sense oligonucleotide and oseltamivir (Tamiflu®), an influenza virus 
neuraminidase inhibitor.

1.5.1. Polymerase inhibitors

Viral enzymes (polymerase + protease + integrase) represent the 
main protein targets of antiviral agents. Inhibitors of viral enzymes 
account for more than two-thirds of all antivirals including virus- and 
host-targeting agents approved between 1987 and 2017 (Fig. 4B). With 
27 approved NMEs, polymerase inhibitors represent the largest class of 
virus-targeting agents (Fig. 4B). Polymerase inhibitors fall into two 
categories: nucleoside analogs and non-nucleoside inhibitors. Although 
idoxuridine (Retrovir®) was the first nucleoside analog approved for 
HIV-1 treatment, other nucleoside analogs used as virus-targeting an-
timetabolites such as acyclovir (Zovirax®) for HSV had already been 
approved. Nucleoside analogs are prodrugs that mimic natural nu-
cleosides and are used, in their triphosphate forms, as substrates for the 
synthesis of viral nucleic acid. This means that nucleoside analogs must 
not only be substrates for viral polymerases, they also need to be re-
cognized and phosphorylated by host nucleo(s/t)ide kinases. Long-term 
use of first-generation anti-HIV nucleoside analogs zalcitabine (Hivid®) 
and didanosine (Videx®) has been limited by acute toxicity due to in-
sufficient selectivity between viral and human DNA polymerases 
(Johnson et al., 2001). Second-generation HIV-nucleosides such as la-
mivudine (Epivir®), emtricitabine (Emtriva®), and tenofovir disoproxil 
fumarate (Viread®) displayed greater selectivity and tolerability. Non-
nucleoside polymerase inhibitors typically bind to allosteric pockets 
distinct from the enzyme active site. In 1996, the anti-HIV compound 
nevirapine (Viramune®) became the first non-nucleoside polymerase 
inhibitor to receive FDA approval. Since then, four more non-nucleo-
side polymerase inhibitors have been approved for HIV-1 treatment: delavirdine mesylate (Rescriptor®), efavirenz (Sustiva®), etravirine (In-
telence®) and rilpivirine hydrochloride (Edurant®) (Sluis-Cremer, 2014).
Dasabuvir (Exviera®) is currently the only non-nucleoside polymerase 
inhibitor approved for the treatment of HCV infection.

1.5.2. Protease inhibitors

With 17 approved NMEs, protease inhibitors represent the second 
most prevalent class of antivirals after polymerase inhibitors. Protease 
inhibitors block an essential maturation step in polyprotein processing 
that is common to many viruses and involve viral proteases. Ten HIV-1 
protease inhibitors have been commercialized: saquinavir mesylate (Invirase®), indinavir sulfate (Crixivan®), ritonavir (Norvir®), nelfinavir 
mesylate (Viracept®), amprenavir (Agenerase®), fosamprenavir calcium (Lexiva®), lopinavir (Kaletra®), atazanavir (Reyataz®), tipranavir 
(Aptivus®), and darunavir (Prezista®) (Lv et al., 2015). The first HIV-1 
inhibitor approved, saquinavir (Invirase®), resulting from peptidomi-
metic design, was approved in 1995. In combination with ritonavir 
boosting, more recently approved protease inhibitors such as atazanavir 
ard darunavir aim to increase potency and bioavailability and reduce
1.5.4. NS5A inhibitors

NS5A is a dimeric membrane protein that interacts with viral RNA and the HCV non-structural protein NS5A has no enzymatic activity. NS5A inhibitors, the first NS5A inhibitors to receive FDA approval in 2014/2015 (Fig. 1). They were soon followed by approvals of ombitasvir (Viekira Pak®), voxlaprevir (Epclusa®), pibrentasvir (Mavyret®), and elbasvir (Zepatier®) in 2016 and 2017. All NS5A inhibitors share a similar NS5A binding site and exquisite in vitro antiviral potencies in the picomolar range, translating to impressive viral load reduction and cure rate in patients (Gao et al., 2016).

2. Forecast for 2018 and beyond

2.1. Changes in trends compared with approved drugs

As of January 2018, a total of 100 active drug candidates are in active development spanning 29 Phase 1, 46 Phase 2, and 25 Phase 3 human clinical trials (Fig. 5A). Of these clinical-stage drug candidates, 25 programs target HIV, 30 are for HBV, and 6 are for HCV (Table 2). An increase in focus toward respiratory infections is supported by 9 and 9 compounds under evaluation to treat influenza and RSV infections, respectively. Although virus-targeting agents continue to dominate the clinical landscape, the number of candidates with host-targeting mechanisms has increased significantly from 14% of approved antivirals to 27% of all antiviral clinical candidates (Fig. 5B). Similarly, small molecules continue to represent the major class of antiviral candidates, although a net increase in the number of biologics and oligonucleotide candidates has occurred relative to approved antiviral drugs. Finally, a large majority (~91%) of antiviral clinical candidates are developed as monotherapeutic agents rather than combination therapies, which could be simply the result of the surge in new indications under evaluation (such as RSV, dengue, smallpox), new mechanisms of actions being exploited for intervention, and first-in-class molecules in development. In most of these cases, first-in-class therapies will have to be approved first as monotherapies before being combined with other agents.

2.2. The radical evolution of future HIV therapeutics

Adherence remains a problem for combination antiretroviral therapies requiring life-long daily oral medications. Lack of adherence can result in suboptimal drug exposure and development of viral mutations associated with drug resistance. To address these limitations, there are now three injectable long-acting antiretrovirals under clinical development as alternatives to daily oral regimens (Jacobson and Flexner, 2017; Margolis and Bobo, 2015). In addition, MK8591 (EdfA) is a clinical-stage nucleoside reverse transcriptase inhibitor (NRTI) with extremely long half-life compatible with weekly oral or even monthly parenteral dosing. Reformulation of Rilpivirine and Cabotegravir to intramuscular nanoparticle delivery also provides pharmacokinetic coverage allowing long-acting weekly injections (Table 2).

Another significant evolution in HIV therapeutics is the intense effort towards evaluation of entry inhibitors. Fostemsavir is a small molecule that blocks gp120 attachment to CD4 T-cells. Broadly neutralizing monoclonal antibodies are also currently being considered as entry inhibitors (Caskey et al., 2016). These experimental drugs include ibalizumab, PRO 140, UB-421, PGT-121, GS-9722, and VRC01LS, which share a similar mechanism consisting in preventing virus attachment to CD4 receptor. Although the utility of these novel antivirals remains to be fully defined, broadly neutralizing antibody could provide an alternative to current oral treatments and also may open the door to long-acting regimen because of their extended half-lives.

Gene therapies are also being evaluated in the clinic as new generations of HIV therapeutics. CAL-1 is a dual therapeutic lentiviral vector that downregulates CCR5 expression of transduced cells via RNA interference (RNAi) and also targets X4-tropic HIV-1, with the goal to control HIV infection after a single treatment (Burke et al., 2015). SB-
728-T uses a zinc-finger based nuclease approach to edit the CCR5 gene and alter the corresponding receptor, making corresponding autologous CD4 T-cells resistant to HIV infection (Tebas et al., 2014) (Table 2).

### 2.3. Second-generation HBV therapeutics

Multiple novel therapeutic approaches are being evaluated in an effort to find more effective therapies for the management or cure of chronic hepatitis B. These include, for example, hepatitis B surface antigen (HBsAg) blockers such as the neutralizing HBV human immunoglobulin GC1102, and the peptide Hepalatide. In addition, REP 2139 is a phosphorothioated oligonucleotide targeting HBsAg release (Table 2) (Fung et al., 2016). Silencing oligonucleotides that target HBV mRNA such as ARB-1467, GSK3389404, GSK-3228836, and RG6004 are also progressing into Phase 2 proof-of-concept studies. One clinical program focuses on targeting the host-based protein bile acids regulating farnesoid X receptor (FXR) with EYP001, a synthetic FXR agonist.

Capsid assembly modulators (CAMs) represent a major class of novel HBV inhibitors. CAMs currently in clinical trial evaluation are JNJ379, RG7907, AB-423, and ABI-H0731 (Table 2). The viral capsid is formed by the core protein that has multiple functions in HBV replication. CAMs accelerate the kinetics of core oligomerization and prevent encapsidation of the polymerase-pregenomic RNA, resulting in a genome-free capsid and reduction of covalently closed circular DNA (cccDNA) (Berke et al., 2017). This dual mode of action is believed to differentiate from previously approved nucleoside analogs and may be key to achieving higher functional cure rates when given alone or in combination with current standard of care.

Chronic HBV infection often results in weak or absent virus-specific T-cell reactivity, a phenomenon now better understood and referred to as T-cell exhaustion (Ye et al., 2015). Immunotherapies provide a novel approach to counteract T-cell exhaustion and enhance clearance of HBV-infected cells. Iniragivir (SB 9200) is a dinucleotide in Phase 2 clinical trials that is claimed to induce interferon signaling pathways by binding to the cellular proteins retinoic acid-inducible gene 1 (RIG-I) and nucleotide-binding oligomerization domain-containing protein 2 (NOD2) (Table 2). Since TLR 7 stimulation also mediates type I interferon signaling, TLR7 agonists AL-034, GS-9688, RG7854, and RO6870868 (RG 7863) are currently being evaluated for the treatment of chronic HBV infection.
| Name                        | Indication | Phase | Type       | Mono/Combo | Company                                      | NCT or other references |
|-----------------------------|------------|-------|------------|------------|----------------------------------------------|--------------------------|
| ABI-H07731 (CpAM)           | HBV        | 2     | Small Molecule | Mono       | Assembly Biosciences                         | NCT03109730              |
| ARB-1467                    | HBV        | 2     | Oligonucleotide | Mono       | Arbutus Biopharma                            | NCT02631096              |
| AB-423                      | HBV        | 1     | Small Molecule | Mono       | Arbutus Biopharma                            | http://bit.ly/2GShPvO     |
| ALN-185                     | HBV        | 2     | Oligonucleotide | Mono       | Alnylam Pharmaceuticals                       | NCT00286038              |
| Morphophiadine              | HBV        | 2     | Small Molecule | Mono       | IEC Pharm                                    | ChiCTR-IR-16008284       |
| AL-034                      | HBV        | 1     | Small Molecule | Mono       | Janssen Pharmaceuticals                       | NCT03285620              |
| RO6870868                   | HBV        | 2     | Small Molecule | Combo      | Roche                                        | NCT02391805              |
| Tenoflovir Exalidex         | HBV        | 2     | Small Molecule | Mono       | Contravir                                    | NCT02716064              |
| Inarigavir (SB 9200)        | HBV        | 2     | Small Molecule | Combo      | Spring Bank                                   | NCT02751996              |
| REP 2139                    | HBV        | 2     | Oligonucleotide | Mono       | Replicor Inc.                                | NCT02233075              |
| REP 2165                    | HBV        | 2     | Oligonucleotide | Mono       | Replicor Inc.                                | NCT02565719              |
| GSK-3389404                 | HBV        | 2     | Oligonucleotide | Mono       | Roche                                        | NCT03020745              |
| GSK-3228836                 | HBV        | 2     | Oligonucleotide | Mono       | GlaxoSmithKline                              | NCT02981602              |
| JNJ-379                     | HBV        | 1     | Small Molecule | Mono       | Janssen Pharmaceuticals                       | NCT03361956              |
| RG-7907                     | HBV        | 1     | Small Molecule | Mono       | Roche                                        | NCT02952924              |
| GS-9688                     | HBV        | 1     | Small Molecule | Mono       | Gilead Sciences                              | ACTRN12617000235303      |
| RG-6004                     | HBV        | 1     | Oligonucleotide | Mono       | Roche                                        | NCT03038113              |
| RG-7854                     | HBV        | 1     | Small Molecule | Mono       | Roche                                        | NCT02956850              |
| INO-9112                    | HBV        | 1     | Small Molecule | Mono       | Roche/Novio                                  | NCT02431312              |
| GS-5801                     | HBV        | 1     | Small Molecule | Mono       | Gilead Sciences                              | ACTRN12616001260415      |
| Myrcludex B                 | HBV        | 2     | Peptide       | Mono       | MYR Pharma                                   | NCT02637999              |
| EVP-001                     | HBV        | 1     | Small Molecule | Mono       | Enoy Pharma                                  | NCT03272009              |
| GC1102                      | HBV        | 2     | Protein       | Mono       | Guangzhou Green Cross                       | NCT02304315              |
| Hepalatide (L47)            | HBV        | 2     | Protein       | Mono       | Shanghai HEP Pharmaceuticals                  | NCT02612506              |
| Besifovir                   | HBV        | 3     | Small Molecule | Mono       | B-Dong                                       | NCT02792088              |
| Tenoflovir disoproxil orotate | HBV    | 3     | Small Molecule | Mono       | 816. 817. Dong-A ST                          | 816. NCT02967939         |
| Tenoflovir disoproxil aspartate | HBV | 3     | Small Molecule | Mono       | Chong Kun Dang                               | NCT02805738              |
| QL-007                      | HBV        | 1     | Small Molecule | Mono       | QiU Pharmaceuticals                           | NCT03244808              |
| APG-1387                    | HBV        | 1     | Small Molecule | Mono       | Asteage Pharma                               | NCT03386526              |
| AT-527                      | HCV        | 1     | Small Molecule | Mono       | Ateas Pharmaceuticals                        | NCT03219957              |
| Faldaprevir                 | HCV        | 3     | Small Molecule | Mono       | Trek Therapeutics/Boehringer Ingelheim       | NCT02716428              |
| VX-222                      | HCV        | 2     | Small Molecule | Mono       | Trek Therapeutics/Vertex                     | NCT01516918              |
| VX-497                      | HCV        | 2     | Small Molecule | Mono       | Trek Therapeutics/Vertex                     | NCT00088504              |
| Ravidasvir                  | HCV        | 2     | Small Molecule | Mono       | Presidio                                     | NCT02961426              |
| TD-6450                     | HCV        | 2     | Small Molecule | Mono       | Trek Therapeutics/Teravance                  | NCT02716428              |
| ABX464                      | HIV        | 2     | Small Molecule | Mono       | Abivax                                       | NCT02990325              |
| Bictegravir/F/TAF            | HCV        | 3     | Small Molecule | Combo      | Gilead Sciences                              | NCT02603107              |
| LA cabotegravir             | HIV        | 3     | Small Molecule | Mono       | ViIV Healthcare                              | NCT02478463              |
| LA cabotegravir + LA ripivirine | HIV   | 3     | Small Molecule | Combo      | Janssen/ViIV Healthcare                       | NCT02901052              |
| Darunavir STR darunavir/cobicistat/emtricitabine/tenofovir alafenamide (Symtuza®) | HIV | 3     | Small Molecule | Combo      | Janssen Pharmaceuticals                       | NCT02578550              |
| dolutegravir + lamivudine   | HIV        | 3     | Small Molecule | Mono       | ViIV Healthcare                              | NCT02211482              |
| Doravirine                  | HIV        | 3     | Small Molecule | Mono       | Merck                                        | NCT02275780              |
| Doravirine/lamivudine/tenofovir disoproxil fumarate | HIV | 3     | Small Molecule | Combo      | Merck                                        | NCT03332095              |
| Etelavirurine               | HIV        | 3     | Small Molecule | Mono       | Viiriom                                      | NCT02489461              |
| Fostemsavir                 | HIV        | 3     | Small Molecule | Mono       | ViIV Healthcare                              | NCT01384734              |
| Ibalizumab                  | HIV        | 3     | Protein       | Mono       | US TaliMed Biologies                         | NCT02707861              |
| PRO 140                     | HIV        | 3     | Protein       | Mono       | CytoDyn                                      | NCT02483078              |
| BIT-225                     | HIV        | 2     | Small Molecule | Mono       | United Biopharma                            | NCT03045861              |
| SB-728-T                    | HIV        | 2     | Gene Therapy  | Mono       | Sangamo Therapeutics                         | NCT01543152              |
| UB-421                      | HIV        | 3     | Protein       | Mono       | United Biopharma                            | NCT02361302               |
| MK8591                      | HIV        | 1     | Small Molecule | Mono       | Merck                                        | NCT02369146              |
| ALT-803                     | HIV        | 1     | Protein       | Mono       | Aalter BioScience                            | NCT03272347              |
| Vesatolimod (GS-9620)       | HIV        | 1     | Small Molecule | Mono       | Gilead Sciences                              | NCT02191098              |
| TMB-607                     | HIV        | 1     | Small Molecule | Mono       | TaiMed Biologies                             | NCT02858401              |
| VRC011LS                    | HIV        | 1     | Protein       | Mono       | Xencor/NIH                                   | NCT03110549              |
| CAL-1                       | HIV        | 2     | Gene Therapy  | Mono       | Calimmune                                    | NCT02797171              |
| GS-9722                     | HIV        | 1     | Protein       | Mono       | Gilead Sciences                              | NCT02390297              |
| MC-4250                     | HIV        | 1     | Small Molecule | Mono       | Merck                                        | NCT02370448              |
| PGT-121                     | HIV        | 1     | Protein       | Mono       | Theracence Sciences                          | NCT03351699              |
| Baloxavir marboxil (Xofluza®) | Influenza | 3     | Small Molecule | Mono       | Roche (Shionogi)                             | NCT02954354              |
| VIS-410                     | Influenza  | 3     | Protein       | Mono       | Visterra                                     | NCT03040413              |
| Medi-8852                   | Influenza  | 2     | Protein       | Mono       | AstraZeneca                                  | NCT02603952              |

(continued on next page)
2.4. Emergence of drugs against respiratory infections

The need for new therapeutic options against influenza virus remains high despite existing vaccines and antivirals. Novel polymerase inhibitors are currently in late-stage clinical development. The nucleoside analog Favipiravir (T-705, AVIGAN®) has been approved in Japan for the treatment of influenza infection limited to cases in which other anti-flu drug are ineffective. There is to our knowledge no indication that favipiravir is currently being developed in the United States or elsewhere. Baloxavir marboxil and pimodivir, both in Phase 3 studies in the United States as of January 2018, target the polymerase acidic (PA) and polymerase basic 2 (PB2) subunit of influenza virus polymerase, respectively (Table 2). Both compounds prevent the virus from hijacking the host capped mRNA and block transcription of viral genes.

The emergence of RSV inhibitors in the clinical pipeline is justified by years of unsuccessful vaccine attempts, combined with a high medical need unaddressed by palivizumab prophylactic treatment in young children and newborns. RSV has become a major respiratory pathogen, especially in young children and newborns, and has been a significant cause of mortality and morbidity in this population. The lack of effective antiviral therapy for RSV is a significant unmet medical need. Several RSV inhibitors are currently in clinical development, including pimodivir, pimodivir/salt, and Baloxavir marboxil, all of which are in Phase 3 clinical trials. Pimodivir, a nucleoside analog, is approved in Japan for the treatment of RSV infection in children under 2 years of age.

### Table 2 (continued)

| Name                  | Indication       | Phase | Type       | Mono/Combo | Company                  | NCT or other references |
|-----------------------|------------------|-------|------------|------------|--------------------------|-------------------------|
| Pimodivir (INJ-872)   | Influenza        | 3     | Small Molecule | Mono       | Janssen Pharmaceuticals  | NCT03376321             |
| INJ-5806              | Influenza        | 2     | Small Molecule | Mono       | Janssen Pharmaceuticals  | NCT03411421             |
| NT-300                | Influenza        | 3     | Small Molecule | Mono       | Romark Laboratories      | NCT03336619             |
| Fludase               | Influenza        | 2     | Protein     | Mono       | Aviragen                | NCT02014649             |
| Laminarivir Octanoate | Influenza        | 2     | Small Molecule | Mono       | Aviragen                | NCT02014649             |
| Radaviren             | Influenza        | 1     | Oligonucleotide | Mono       | Sarepta Therapeutics    | NCT01747148             |
| RV-521                | RSV              | 2     | Small Molecule | Mono       | ReViral                 | NCT03258502             |
| Presatovir (GS-5806)  | RSV              | 2     | Small Molecule | Mono       | Gilead Sciences         | NCT02534350             |
| Luminosibine (ALS-8176)| RSV            | 2     | Small Molecule | Mono       | Janssen Pharmaceuticals  | NCT02935673             |
| ALK-0117              | RSV              | 2     | Protein     | Mono       | Abylynx                 | NCT02979431             |
| AK0529                | RSV              | 2     | Small Molecule | Mono       | Ark Biosciences         | NCT03400995             |
| INJ-678               | RSV              | 2     | Small Molecule | Mono       | Janssen Pharmaceuticals  | NCT02593851             |
| MEDI88897             | RSV              | 2     | Protein     | Mono       | AstraZeneca             | NCT02878330             |
| PC-786                | RSV              | 1     | Small Molecule | Mono       | Pulmocide               | NCT03382431             |
| EDP-938               | RSV              | 1     | Small Molecule | Mono       | Enanta Pharmaceuticals  | NCT03384823             |
| GS-5734               | Ebola Virus      | 2     | Small Molecule | Mono       | Gilead Sciences         | NCT02818582             |
| BTA074                | HPV              | 2     | Small Molecule | Mono       | Abylynx                 | NCT01512102             |
| Pritelivir            | HSV              | 2     | Small Molecule | Mono       | Alc Naked              | NCT03073967             |
| Ranipimase            | HPV              | 2     | Small Molecule | Mono       | Tamir Biotechnology     | NCT02535104             |
| DSAS181              | Influenza Virus  | 3     | Protein     | Mono       | Janssen Pharmaceuticals  | NCT01644877             |
| AT-129                | Epstein-Barr Virus | 2       | Cell Therapy | Mono       | Atara Biotechnologies    | NCT03392142             |
| Tecovirimat           | Smallpox (Variola Virus) | 3       | Small Molecule | Mono   | SIGA                     | NCT02080767             |
| Modipafant            | Dengue Virus     | 2     | Small Molecule | Mono       | 60 Degrees Pharmaceutical | NCT02569827             |
| Cegalovir            | Dengue Virus     | 2     | Small Molecule | Mono       | 60 Degrees Pharmaceutical | NCT02569827             |
| Maribavir (SHP-620)   | CMV              | 3     | Small Molecule | Mono       | Shire Pharmaceuticals   | NCT02931539             |
| Cyclopropavir (MBX-400)| CMV            | 1     | Small Molecule | Mono       | Microbiotix Inc.        | NCT02454699             |
| SHP-640              | Adenoviral Conjunctivitis | 3       | Small Molecule | Combo | Shire Pharmaceuticals   | NCT02998554             |
| Brincidofovir         | Adenovirus/Smallpox (Variola Virus)/CMV | 2/3    | Small Molecule | Mono   | Chimerix                | NCT02596997             |
| Viralym M            | CMV, AdV, BKV, EBV HHV-6 | 2       | Cell Therapy | Mono       | Viral Cytex             | NCT02765802             |
| Viralym C            | CMV              | 1     | Cell Therapy | Mono       | Viral Cytex             | NCT02313857             |
| Lonafarnib            | HDV              | 2     | Small Molecule | Mono       | Eiger Biopharma         | NCT02527707             |
| Pegylated-interferon-lambda (PEG-IFN-λ) | HDV | 2     | Protein     | Mono       | Eiger Biopharma         | NCT02765802             |
| SB206                | HPV              | 2     | Small Molecule | Mono       | Novan Therapeutics      | NCT03436615             |
| VP-102               | HPV              | 2     | Small Molecule | Mono       | Verrica Pharmaceuticals | NCT03377803             |
| SAB-301              | Corona-virus     | 1     | Protein     | Mono       | SAB Biotherapeutics     | NCT02788188             |
| ZMapp                | Ebola Virus      | 1     | Protein     | Mono       | Mapp Biopharma          | NCT02389192             |

**Viruses.**

HIV-1 = Human immunodeficiency virus-1.

HCV = Hepatitis C virus.

HBV = Hepatitis B virus.

HDV = Hepatitis D virus.

CMV = Cytomegalovirus.

HSV = Herpes simplex virus.

HPV = Human papillomavirus.

AdV = Adenovirus.

BKV = BK virus.

EBV = Epstein-Barr virus.

HHV-6 = Human herpesvirus-6.

Other abbreviations.

Mono = Monotherapy.

Combo = Combination therapy.

2.4. Emergence of drugs against respiratory infections

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The emergence of RSV inhibitors in the clinical pipeline is justified by years of unsuccessful vaccine attempts, combined with a high medical need unaddressed by palivizumab prophylactic treatment in young children and newborns. Several RSV inhibitors are currently in clinical development, including pimodivir, pimodivir/salt, and Baloxavir marboxil, all of which are in Phase 3 clinical trials. Pimodivir, a nucleoside analog, is approved in Japan for the treatment of RSV infection in children under 2 years of age.
high-risk infants. Currently, three classes of RSV inhibitors are in clinical development. Second-generation monoclonal antibodies represent the first class of RSV inhibitors. MEDI8897, a recombinant monoclonal antibody with a modified Fc region that extends its half-life, is being developed for RSV prophylaxis for all infants (Griffin et al., 2017). ALX-0171 is a trivalent nanobody that targets the RSV Fusion (F) protein for delivery via inhalation (Detalle et al., 2015). Fusion inhibitors, the second class of novel RSV inhibitors, block an essential conformational change of the RSV F protein, thereby inhibiting cell entry by preventing fusion between the virus envelope and the host-cell membrane (Rojas et al., 2017). Current fusion inhibitors include N1N-678, presatovir (GS-5806), AK0529, and RV521 (Table 2). Replication inhibitors represent the third class of RSV drug candidates. Lumicitabine and PC-786 bind to the polymerase L subunit (Deval et al., 2015; Coates et al., 2017), whereas EDP-938 interferes with the nucleoprotein N. Lumicitabine is currently the only RSV replication inhibitor with demonstrated clinical proof-of-concept efficacy (DeVincenzo et al., 2015).

2.5. Experimental treatments for other acute viral infections

2.5.1. Ebola

The recent Ebola virus outbreak in West Africa during 2013–2016 triggered intense efforts to identify novel inhibitors for filoviruses. BCX4430 and favipiravir, two nucleoside analogs with a relatively broad spectrum activity once considered for treatment of Ebola virus disease, are no longer under clinical development (Siskoko et al., 2016). M2map is a combination of 3 humanized antibodies produced in genetically-modified tobacco plants and targets 3 Ebola glycoprotein epitopes. ZMap was tested in the clinic during the West Africa Ebola outbreak. Although ZMapp seemed to be beneficial, the results did not meet statistical significance for efficacy (Group et al., 2016). The new research and development efforts also resulted in the identification of GS-5734, a nucleotide analog polymerase inhibitor with broad antiviral spectrum activity (Warr et al., 2016). Following Phase 1 safety studies, GS-5734 was first given to two patients, one in the United Kingdom in October 2015 and one in Guinea the following month, through a compassionate use request (Jacob et al., 2016; Dornemann et al., 2017). The current Phase 2 study aims to evaluate the antiviral efficacy of 5 days of GS-5734 given intravenously to male Ebola virus disease survivors shedding Ebola virus in their semen (Table 2).

2.5.2. Dengue

Currently no drugs are approved for the treatment of dengue virus infection. Modipafant and celsigivir are currently in Phase 2 clinical trials for the treatment of adults with dengue infection presenting within 48 h of fever onset. Modipafant is an antagonist of activation of the platelet-activating factor receptor (PAFRA), a host protein believed to be implicated in the pathogenesis of severe dengue infection through inflammation. Celsigivir is derived from a natural product and is also a host-targeting agent that inhibits alpha-glucosidase I, which is needed for the folding of viral glycoproteins. These two compounds were selected for clinical development because their safety has previously been demonstrated in humans and because they inhibit dengue virus replication in vitro and improve survival in a lethal mouse efficacy model (Souza et al., 2009; Rathore et al., 2011).

2.5.3. Smallpox (variola virus)

The development of smallpox inhibitors has been rationalized by the need to stockpile agents aimed to contain potential future bio-threats. Brincidofovir is a lipid-conjugated prodrug of cidofovir, an acyclic nucleoside analog with broad antiviral spectrum against DNA and RNA viruses. Brincidofovir is currently in clinical evaluation for the treatment of smallpox infection for biodefense applications, and in Phase 2 for the treatment of adenovirus in pediatric stem cell transplant recipients. Brincidofovir is being developed for smallpox under the FDA’s Animal Rule, which allows for testing of investigational drugs in animal models to support effectiveness in diseases that are not ethical or feasible to study in humans. Tecovirimat is also being developed for smallpox under the Animal Rule for smallpox biodefense applications. Tecovirimat was identified via a high-throughput screen of a small molecule chemical library and has been shown to protect nonhuman primates from smallpox infection (Mucker et al., 2013). Tecovirimat inhibits p37, a viral protein involved as virulence factor in the formation of enveloped virions.

3. Driving forces for innovation in antiviral research

Although the discovery of each antiviral drug has a unique story and distinct circumstances that may not apply to other programs, this section aims to identify guidelines or examples of attributes that drive success in identifying and developing antiviral drugs.

3.1. Biological breakthroughs: first-in-class

Breakthroughs in basic biological and biochemical science can lead to the acceleration of antiviral research and provide a springboard to drug discovery applications. A striking example is the establishment of a robust cell culture surrogate system for HCV replication. Although HCV was first isolated and identified in 1989, attempts to grow the virus in cell culture were unsuccessful and greatly limited the ability to evaluate novel antiviral therapies. Ten years of research were needed to develop a subgenomic replicon system that captured the functionality of the non-structural proteins and recapitulated the intracellular steps of viral genomic replication (for review: (Kauf et al., 2009)). Because the HCV replicon was used extensively as a primary screen for antiviral testing, establishing this cell culture system was key to the discovery of all current HCV direct acting agents. This is particularly true in cases where biochemical or structural biology tools were not available to assist medicinal chemistry efforts. The discovery of daclatasvir, the first approved HCV NS5A inhibitor, resulted from a high-throughput screen using the HCV replicon assay (Belema and Meanwell, 2014).

Targeted phenotypic screens have become major contributors to the understanding of novel mechanisms of inhibition leading to differentiated antiviral programs. The flu inhibitor pemivodivir was identified using a phenotypic screen under conditions of high multiplicity of infection (MOI) in which oseltamivir is not active. This targeted screen approach was key to differentiating novel PB2 inhibitors, largely MOI independent, from other classes of anti-flu agents that prevent virus replication only at the early stage of infection (Byrn et al., 2015). Fluorescence microscopy has also been used in conjunction with high-throughput screening to identify phenotypic changes associated with antiviral effects. Nucleozin, a preclinical first-in-class influenza inhibitor, was first characterized by its ability to block the nuclear accumulation of nucleoprotein in infected cells (Kao et al., 2010). Considering the growing use of high-content imaging for antiviral testing (Mudhasani et al., 2015; Watterson et al., 2016), it is likely that targeted phenotypic screens with early access to mechanism of action information will have an increasingly important role in antiviral drug discovery. These examples also show that, in many cases, the discovery of first-in-class antiviral drugs has its roots in biological innovations and ingenious use of novel in vitro assays.

3.2. Chemical innovation: best-in-class

The analysis of all antiviral drug approvals over the last 30 years reveals many examples of best-in-class programs that follow approved drugs or more advanced clinical candidates. As we detailed earlier in this review (e.g., polymerase and protease inhibitors), second- or third-generation HIV and HCV small molecule therapeutics have led to best-in-class drug approvals, providing the foundations for current standards of care. In these cases, research programs tend to leverage the biological advances made with first-in-class prototype molecules, and focus on
chemical innovation through follow-on or back-up approaches (Schulze and Ringel, 2013). Different strategies have been used to foster best-in-class innovation for small molecules, sometimes relying on competitive intelligence (i.e., “patent busting”). In all cases, best-in-class “fast-follow” antiviral programs result from intensified medicinal chemistry efforts aimed at addressing the shortcomings of the first-generation drugs: intrinsic binding or inhibition potency, strain/genotype/resistance mutation potency coverage, safety, or convenience. For example, the anti-HCV drug sofosbuvir is a monophosphate nucleoside prodrug as a follow-on to the first-generation molecule mericitabine. Sofosbuvir was designed to improve metabolic activation leading to the higher liver triphosphate formation by evading the first and limiting kinase phosphorylation step (Murakami et al., 2008). Similarly, the HIV-1 drug etravirine was designed to overcome suboptimal potency and drug resistance mutations associated with first-generation non-nucleoside reverse transcriptase inhibitors (Das et al., 2004). In the latter case, X-ray crystallography of the reverse transcriptase target provided valuable information for a structure-based drug design approach. Fragment screening and expansion campaigns have also contributed to the discovery of novel chemical starting points aimed at identifying next-generation antivirals. For example, crystallographic fragment screening of HIV integrase binders recently led to the discovery of novel allosteric inhibitors for the protein target (Patel et al., 2016). More generally, structural biology has proven to be a valuable tool in antiviral research to optimize ligand efficiency and therefore improve potency of inhibitors interacting with well-defined molecular targets.

3.3. Clinical innovation

One of the main challenges in the development of antiviral medicines targeting acute viral infections is the limited time window for therapeutic intervention, which may greatly fluctuate depending on the virus, patient population, and mode of action of the drug candidate. This is particularly problematic for first-in-class drug candidates targeting novel and therefore clinically unproven targets or pathways. This enormous obstacle to antiviral development has been partly addressed with the introduction of human challenge studies, now commonly used in early RSV and influenza clinical programs to obtain first proof-of-concept efficacy in healthy volunteers and to help design subsequent clinical trials in naturally infected patients (Bagga et al., 2013). Healthy adult volunteers are typically infected with low quantities of virus inoculum under controlled conditions resulting in mild symptoms. Human challenge studies were critical to the clinical development of first-in-class RSV fusion and polymerase inhibitors presatovir and lumicitabine, respectively (DeVincenzo et al., 2014; DeVincenzo et al., 2015).

Another clinical innovation in antiviral research is the increasing use of combination therapies for HIV-1 and HCV therapeutics (Fig. 3B). This was made possible by the availability of single agents with non-overlapping mechanisms of actions and additive or synergistic potential, with a gradual evolution toward best-in-class combinations. Single-tablet regimens using combination therapies represent another major clinical innovation aiming to increase efficacy and adherence to long-term HIV-1 treatment regimens. In comparison with therapies requiring two or more pills per day, once-daily single-tablet regimens were associated with greater adherence, fewer hospitalizations, and lower overall health care costs (Cohen et al., 2013). Considering the recent surge in first-in-class HBV drug candidates with novel mechanisms of action, evaluation of these drug candidates as potential combination treatments should be expected. Likewise, it will be exciting to consider novel combination treatments for respiratory viruses given the recent advances in novel mono therapeutics targeting influenza and RSV. In a Phase 2b study, pimodivir combined with oseltamivir demonstrated a significant reduction in viral load in adults with influenza A (https://www.jnj.com/media-center/press-releases/pimodivir-alone-or-in-com-bination-with-oseltamivir-demonstrated-a-significant-reduction-in-viral-load-in-adults-with-influenza-a).

Finally, the establishment of national programs or organizations such as the National Institute of Allergy and Infectious Diseases (NIAID) have been instrumental to systematically and more efficiently recruit eligible patients for new experimental treatments.

4. Conclusions and perspective

In summary, the analysis of the last 30 years of 88 antiviral drug approvals in the United States demonstrates that a majority of them target chronic infections caused by HIV-1, HBV, HCV, and herpesviruses (HSV and CMV). Only a few drugs were approved to treat acute infections, mainly influenza. A large majority of the approvals were for small molecules and virus-targeting agents over large molecules and host-targeting therapies. The high rate of combination therapy approvals during the last five years is attributed to the rich HIV-1 and HCV drug pipelines that are now reaching maturation with multiple therapeutic options and competing best-in-class molecules. In contrast, 91% of molecules currently in clinical development are under evaluation as monotherapies because they are first-in-class experimental therapies for indications lacking other therapeutic options (Fig. 5B). The current experimental antiviral clinical pipeline also reflects, at least partially, a departure from classical targets (polymerase, protease...) with oligonucleotide-based therapeutics, cell fusion inhibitors, capsid-assembly modulators, and an array of novel host-based mechanisms. In addition, we observe a surge in anti-HIV broadly neutralizing monoclonal antibodies reaching clinical stage evaluation.

The current antiviral clinical pipeline is constantly evolving with new candidates entering development and other clinical programs being terminated. During preparation of this manuscript, the US FDA approved Biktarvy® (bictegravir, emtricitabine, tenofovir alafenamide) on 7 February 2018 for the treatment of HIV-1 infection; on 23 February 2018, Xofluza® (baloxavir marboxil) received Japanese regulatory approval for use against influenza infection. On 6 March 2018, the FDA approved the anti-COVID-19 monoclonal antibody Trogarzo® (iba lizumab) for heavily treatment-experienced adult HIV patients at risk of failing other antiretroviral therapies.

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