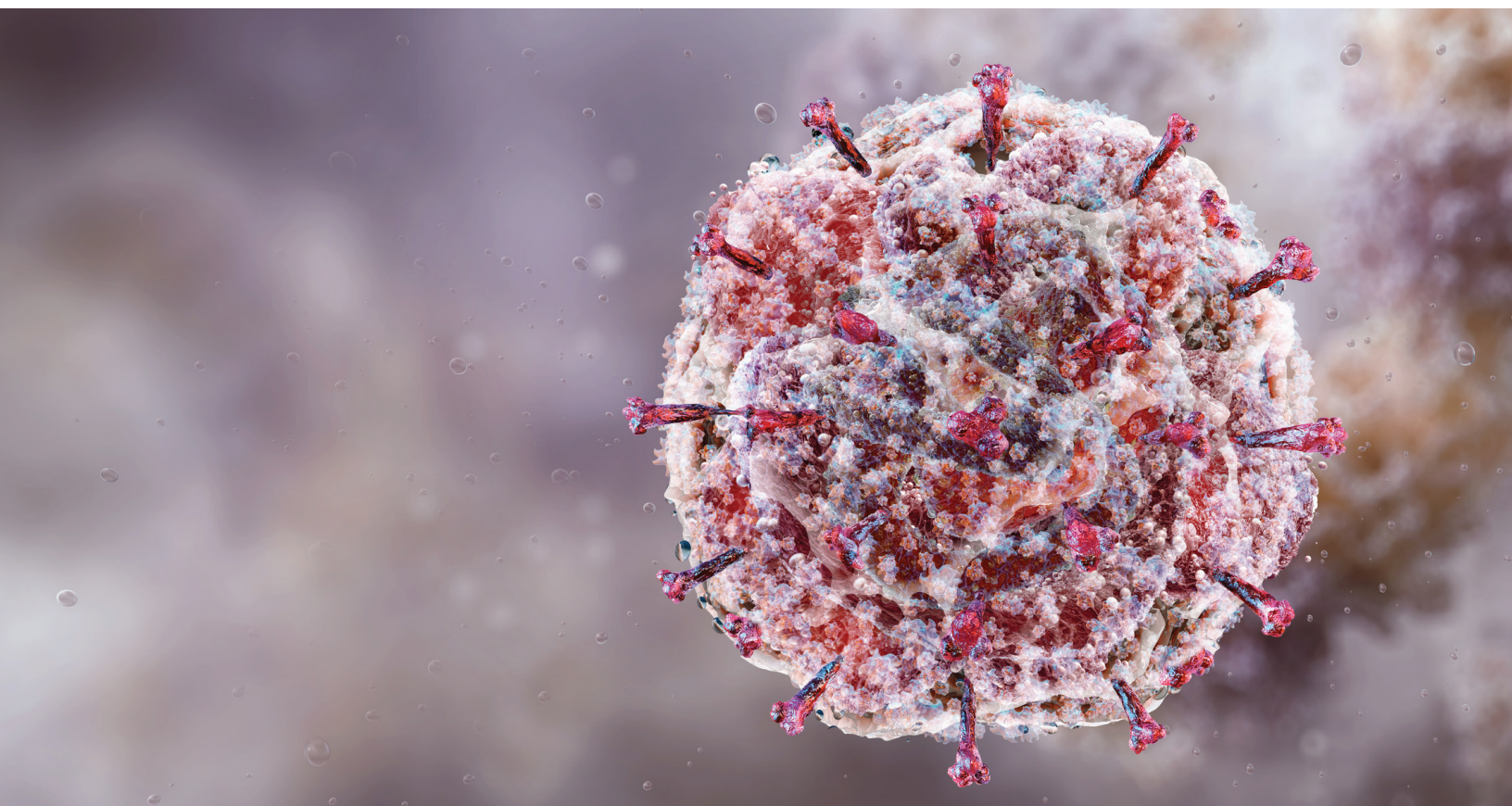


HOW ANTIVIRAL DRUGS WORK

MECHANISMS OF ACTION, RESISTANCE AND DEVELOPMENT CONSIDERATIONS

AT QPS WE BELIEVE IN DEVELOPING CLOSE AND LONG-LASTING RELATIONSHIPS WITH OUR CLIENTS ON THE BASIS OF TRUST AND MUTUAL RESPECT.

This mutual trust, combined with the agile approach we offer as a specialty CRO, helps improve the quality of your outsourced clinical work and reduces the degree of required oversight.



INTRODUCTION

Antiviral drugs play a central role in treating viral infections, reducing disease progression and preparing for future outbreaks. While vaccines can help prevent infection, antiviral therapies remain essential for patients who become infected, are immunocompromised, are unvaccinated or face viral variants that may reduce vaccine effectiveness. Antiviral drug development strategies emphasize the continued need for antiviral reserves, broader therapeutic strategies and innovation in response to emerging pathogens.

Unlike bacteria, viruses cannot replicate independently. They carry DNA or RNA and rely on host cells to reproduce. This dependency creates opportunities for antiviral intervention, but it also makes drug development difficult. Effective antivirals must interfere with viral replication while minimizing harm to the host.

Antiviral mechanisms of action can be understood as strategic interruptions in the viral life cycle. Some drugs block entry into the host cell. Others prevent uncoating, genome replication, viral protein processing, integration into the host genome or release of new viral particles.

Major antiviral mechanisms include:

- ▶ Entry and fusion inhibition
- ▶ Capsid and uncoating inhibition
- ▶ Polymerase inhibition
- ▶ Reverse transcriptase inhibition
- ▶ Protease inhibition
- ▶ Integrase inhibition
- ▶ Neuraminidase inhibition and polymerase-targeted influenza therapy

As antiviral science advances, drug developers are also exploring host-targeted approaches, immune-modulating strategies, nucleic acid therapeutics, broad-spectrum antivirals, nanotechnology-enabled delivery and AI-guided discovery. For sponsors, the mechanism of action influences a range of factors, including assay strategy, bioanalysis, PK/PD planning, resistance monitoring, patient selection, clinical endpoints and regulatory planning.

This white paper will examine major antiviral mechanisms of action, show how viral biology shapes therapeutic strategy and highlight key development considerations for current and emerging antiviral therapies.

THE VIRAL LIFE CYCLE: A ROADMAP FOR ANTIVIRAL ACTION

The typical life cycle of most viruses proceeds through the following steps.

- ▶ A virus attaches to a host cell through interactions between viral and host surface proteins.
- ▶ The virus enters the cell, releases its genome and uses host machinery to produce viral RNA, DNA and proteins.
- ▶ Depending on the virus, additional steps may include uncoating, reverse transcription, integration or proteolytic processing of viral proteins.
- ▶ New viral components assemble into particles that leave the cell through lysis or budding.

Each step creates a potential drug target. Antiviral drugs can:

- ▶ Block the virus before it enters the cell
- ▶ Prevent the viral genome from being copied
- ▶ Prevent viral proteins from being processed into functional forms
- ▶ Disrupt viral assembly
- ▶ Prevent new viruses from spreading to additional cells

This life-cycle view helps drug developers answer practical questions, such as where the candidate acts, which assays are needed to confirm activity, which viral, immune or clinical endpoints should be measured, how resistance might emerge and what evidence will show that the mechanism translates into clinical benefit.

VIRUSES OF INTEREST: HOW VIRAL BIOLOGY SHAPES ANTIVIRAL STRATEGY

Antiviral development starts with a detailed understanding of viral biology. Viruses differ in genome type, structure, replication strategy, host-cell interactions, tissue preference and disease course. These differences influence how viruses enter cells, where they replicate, how they spread and which assays, models and endpoints may be most relevant during drug development.

One major distinction is genome type. RNA viruses, including HIV, hepatitis C virus (HCV), influenza, Ebola, Marburg and hantaviruses, rely on RNA-based replication strategies and may mutate quickly. DNA viruses, including hepatitis B virus (HBV), human papillomavirus (HPV) and Epstein-Barr virus (EBV), follow different replication patterns and may establish persistent or latent infections. Hepatitis A virus (HAV) is also an RNA virus, but its clinical course and development considerations differ from chronic viral infections such as HBV, HCV and HIV.

Envelope status is another important distinction. Enveloped viruses, including HIV, HBV, HCV, influenza, EBV, Ebola, Marburg and hantaviruses, have a lipid membrane surrounding the viral particle. This envelope helps mediate attachment and entry into host cells. Non-enveloped viruses, such as HAV and HPV, lack this lipid membrane and often rely on different entry, environmental stability and transmission characteristics.

Viral replication strategies also vary. Retroviruses such as HIV use reverse transcription to convert viral RNA into DNA before integration into the host genome. HBV also uses reverse transcription as part of its replication cycle, despite being a DNA virus. Influenza replicates in the nucleus and depends on viral polymerase activity to produce viral RNA. Herpesviruses such as EBV can establish latency,

creating long-term reservoirs that complicate therapeutic strategies.

Together, these examples show why antiviral development must begin with the biology of the virus. The following section examines major direct-acting antiviral mechanisms that interrupt the viral life cycle and inform current and emerging therapeutic strategies.

DIRECT-ACTING ANTIVIRAL MECHANISMS

Direct-acting antivirals target viral structures, enzymes or life-cycle steps. In practice, their development depends on matching the drug candidate to the right viral target, assay system, resistance-monitoring strategy and clinical endpoint. These therapies can be grouped by the stage they interrupt, including viral entry and fusion; capsid function and uncoating; genome replication; reverse transcription; integration; protein processing; and viral release.

Entry and Fusion Inhibitors

Entry and fusion inhibitors act early. They prevent the virus from attaching to or entering the host cell, stopping infection before replication begins.

HIV provides clear examples. Enfuvirtide inhibits HIV fusion by interfering with the gp41 conformational change required for entry. Maraviroc blocks CCR5-mediated HIV entry by preventing viral interaction with a host co-receptor.

Entry and fusion mechanisms are also relevant to many enveloped viruses, respiratory viruses and filoviruses such as Ebola and Marburg.

Development considerations include:

- ▶ Confirming the specific entry step affected, such as attachment, receptor engagement or membrane fusion
- ▶ Selecting cell-based assays that reflect relevant host-cell receptors
- ▶ Evaluating tissue exposure, especially for respiratory or mucosal infections

- ▶ Considering the timing of treatment, since entry inhibitors act before productive replication
- ▶ Assessing combination potential with agents that act later in the viral life cycle

Capsid and Uncoating Inhibitors

The viral capsid protects the viral genome and helps control uncoating, genome delivery, assembly and maturation. Capsid and uncoating inhibitors are designed to disrupt these processes.

Capsid-focused strategies are relevant for HIV and HBV antiviral development. In HIV, capsid inhibition can affect multiple stages of replication, including nuclear import, uncoating and capsid assembly, and lenacapavir has demonstrated the clinical relevance of long-acting capsid-targeted therapy. HBV capsid assembly modulators are another area of continued research and clinical development, with the goal of disrupting nucleocapsid assembly and suppressing viral replication.

Development considerations include:

- ▶ Demonstrating the specific viral life-cycle stage affected
- ▶ Distinguishing effects on uncoating, assembly and maturation
- ▶ Evaluating structural biology and capsid dynamics
- ▶ Monitoring resistance mutations in capsid or related viral proteins

Polymerase Inhibitors

Polymerase inhibitors block enzymes that viruses use to copy DNA or RNA. Nucleoside and nucleotide analogs mimic natural building blocks of viral genomes. Once incorporated into the growing chain, some terminate replication.

Acyclovir and valacyclovir illustrate this approach for herpesviruses. HBV nucleoside and nucleotide analogs, HCV polymerase inhibitors and SARS-CoV-2 replication-targeting agents such as remdesivir show the broader importance of polymerase inhibition across viral diseases.

Development considerations include:

- ▶ Evaluating prodrug activation, when relevant
- ▶ Measuring intracellular metabolites for nucleoside or nucleotide analogs
- ▶ Characterizing viral load kinetics
- ▶ Establishing PK/PD relationships
- ▶ Assessing selectivity for viral versus host polymerases
- ▶ Monitoring resistance mutations in viral polymerase genes

Reverse Transcriptase Inhibitors

Reverse transcriptase inhibitors are especially important in HIV treatment because HIV must convert its RNA genome into DNA before integration into the host genome. Reverse transcriptase inhibitors interrupt this step.

Zidovudine, a nucleoside reverse transcriptase inhibitor, was the first antiretroviral approved for HIV treatment. Current HIV treatment commonly relies on combinations that include nucleoside or nucleotide reverse transcriptase inhibitors along with drugs from other classes.

Development considerations include:

- ▶ Assessing activity against reverse transcription
- ▶ Evaluating a combination therapy strategy
- ▶ Monitoring resistance-associated mutations
- ▶ Supporting long-term safety assessment
- ▶ Measuring the durability of viral suppression

Protease Inhibitors

Many viruses produce proteins as large polyproteins that must be cleaved by viral proteases. Protease inhibitors block this process, preventing the formation of mature, infectious virus.

Protease inhibition is important in HIV, HCV and SARS-CoV-2 treatment. The protease inhibitor nirmatrelvir targets the SARS-CoV-2 main protease and is co-administered with ritonavir, which increases nirmatrelvir exposure.

Development considerations include:

- ▶ Assessing enzyme selectivity
- ▶ Characterizing metabolism
- ▶ Evaluating drug-drug interaction potential
- ▶ Supporting combination regimen design
- ▶ Monitoring resistance mutations near the protease active site

Integrase Inhibitors

Integrase inhibitors prevent viral DNA from being inserted into the host genome. This class is most relevant to retroviruses such as HIV. Integrase strand transfer inhibitors are now a major component of antiretroviral therapy.

Development considerations include:

- ▶ Confirming inhibition of viral integration
- ▶ Evaluating resistance profiles
- ▶ Supporting combination therapy strategy
- ▶ Assessing long-term treatment durability
- ▶ Measuring sustained viral suppression

INFLUENZA ANTIVIRALS: NEURAMINIDASE AND POLYMERASE-TARGETING APPROACHES

Influenza provides an example of how treatment modalities may target multiple points in the viral life cycle. Current FDA-approved influenza antivirals include the neuraminidase inhibitors oseltamivir, zanamivir and peramivir, as well as the polymerase acidic endonuclease inhibitor baloxavir. Baloxavir inhibits viral mRNA synthesis, and neuraminidase inhibitors limit the release and spread of newly formed influenza viruses from infected cells.

Development considerations include:

- ▶ Defining the treatment window
- ▶ Accounting for the route of administration
- ▶ Selecting symptom, virologic and clinical endpoints
- ▶ Measuring viral shedding
- ▶ Evaluating strain susceptibility
- ▶ Monitoring resistance
- ▶ Considering use in populations at higher risk for influenza complications

HOST-TARGETED AND IMMUNE-MODULATING STRATEGIES

Direct-acting antivirals target the virus. Host-targeted antivirals target the cellular factors that viruses depend on. These may include host receptors, co-receptors, kinases, intracellular trafficking pathways, nucleotide synthesis pathways and innate immune signaling systems.

This strategy may offer important advantages. Because host genes are less mutation-prone than viral genomes, host-targeted approaches may create a higher barrier to resistance. They may also support broader activity across related viruses, making them especially relevant for emerging viruses, rapidly mutating pathogens and preparedness-focused antiviral development. Current antiviral drug discovery research identifies viral targets, host targets and viral antagonism of host innate immunity as important categories of antiviral targets.

Examples include host kinases involved in viral trafficking and DHODH, an enzyme in pyrimidine nucleotide synthesis. Viral replication requires nucleotides, so DHODH inhibition can suppress viral genome replication and may support broad-spectrum antiviral activity.

Immune-modulating strategies are another important area. Interferon signaling, RIG-I, cGAS-STING and toll-like receptor pathways help cells recognize viral infection and activate antiviral defenses. These strategies may be especially relevant when viral replication, host response and disease severity are closely linked.

Host-targeted approaches also bring development challenges, including:

- ▶ Safety and tolerability
- ▶ Selectivity
- ▶ Therapeutic window
- ▶ Patient selection
- ▶ Biomarker strategy
- ▶ Potential unintended effects on host biology

RESISTANCE AND DEVELOPMENT CHALLENGES

Resistance is one of the central challenges in antiviral development. Viruses can replicate quickly, allowing mutations that reduce drug susceptibility to emerge under selective pressure. Resistance can affect a single drug, an entire class, combination regimens and future treatment options.

The influenza field provides a practical example of why current treatment guidance matters. Older influenza A M2 inhibitors have become clinically limited due to resistance. Current influenza therapies require ongoing surveillance of susceptibility and resistance.

The mechanism of action shapes development risks and the studies needed to address them. For example:

- ▶ A polymerase inhibitor may require active metabolite analysis and viral load kinetics.
- ▶ A protease inhibitor may require an assessment of drug-drug interactions.
- ▶ A capsid inhibitor may require monitoring for structural escape mutations.
- ▶ An influenza antiviral may require strain susceptibility and resistance surveillance.
- ▶ A host-targeted therapy may require pathway-specific safety monitoring.
- ▶ A combination regimen may require cross-resistance evaluation.

Beyond resistance, antiviral developers face translational and clinical challenges. Promising in vitro or animal-model activity may not translate into human clinical efficacy. Patient selection, endpoint strategy, PK/PD planning, route of administration, treatment timing and regulatory expectations all influence development decisions. These challenges are especially pronounced for acute infections, outbreak-associated pathogens and therapies that target host biology.

EMERGING ANTIVIRAL STRATEGIES

Antiviral development is expanding beyond traditional small-molecule classes. Discovery programs increasingly combine target-based design, phenotypic screening, computational tools and advanced delivery technologies. Together, these approaches reflect a shift toward more integrated discovery strategies that combine biological screening, defined molecular targets, computational modeling and improved delivery.

Important areas of innovation include:

- ▶ Phenotypic screening, which evaluates whether a compound produces a desired biological effect, such as inhibition of viral replication.
- ▶ Target-based drug discovery, which starts with a defined molecular target, such as a viral protease, polymerase or host dependency factor.
- ▶ Structure-guided design, which uses knowledge of target structure to support hit identification and optimization.
- ▶ AI-enabled discovery, which may help predict protein structures, identify drug targets, forecast activity and support de novo drug design.
- ▶ Nanotechnology-enabled delivery, which can support targeted delivery, controlled release and delivery of nucleic acid-based therapies.
- ▶ Nucleic acid therapeutics, including antisense molecules, aptamers and RNA interference agents.
- ▶ Targeted protein or RNA degradation, which may expand the range of druggable antiviral targets.
- ▶ Biomolecular condensate-based discovery, an emerging strategy linked to a new understanding of viral and host cell biology.

Antiviral pipelines are likely to place increasing emphasis on broader-spectrum antivirals, long-acting formulations, combination approaches, host-targeted strategies, pandemic preparedness

platforms and resistance-aware drug design. These approaches will require collaboration across virology, medicinal chemistry, bioanalysis, clinical pharmacology, regulatory strategy and clinical trial operations.

QPS: A PARTNER FOR ANTIVIRAL DRUG DEVELOPMENT

Antiviral drug development requires more than identifying a promising target. Sponsors must show how a candidate works, how it behaves in the body, how it affects viral replication or disease progression and how resistance may emerge.

QPS supports sponsors across antiviral research and drug development with scientific and operational services that help connect mechanism of action to measurable evidence.

QPS can help antiviral drug developers with the following:

- ▶ Nonclinical development support - Generate data to characterize antiviral activity, safety, exposure and development potential
- ▶ Bioanalytical method development and validation - Develop reliable methods to measure drug candidates, metabolites, biomarkers and other critical analytes
- ▶ PK and PK/PD analysis - Connect exposure to antiviral activity, viral load kinetics, safety and dose selection
- ▶ Clinical development support - Support studies designed around acute, chronic or emerging viral infections
- ▶ Assay and biomarker strategy - Align mechanisms of action with the right measurements for decision-making
- ▶ Resistance-aware development planning - Support programs in which baseline resistance, treatment-emergent resistance or cross-resistance may influence clinical strategy
- ▶ Regulatory-aware study execution - Generate high-quality data packages that support development decisions and regulatory interactions
- ▶ Flexible CRO partnership - Adapt to antiviral programs across common infections, chronic viral diseases and emerging viral threats

As antiviral pipelines expand across common infections, chronic viral diseases and high-concern pathogens, sponsors need CRO partners who understand the connection between viral biology and development strategy. QPS brings scientific, operational and collaborative experience to help antiviral developers move programs forward with confidence.

Partner with QPS to advance antiviral development from mechanism to meaningful clinical evidence.

TIME IS OF THE ESSENCE IN DRUG DEVELOPMENT.
CONTACT THE QPS BUSINESS DEVELOPMENT TEAM TODAY!

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