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HOST-DIRECTED ANTIVIRAL STRATEGIES: REPURPOSING DSRNA VIRUSES FOR BROAD-SPECTRUM PANDEMIC RESPONSE

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ABSTRACT

Viral infections are a continuing challenge to the health of the world, because they spread so easily and have a high mutation rate and are becoming resistant to conventional antiviral medications. Antiviral tools are needed to respond quickly to the emergence of new pathogens, as evidenced by the recent epidemics of COVID 19, Ebola and influenza. Traditional antiviral therapies focus on viral proteins and replication mechanism, are, however, often not fully effective due to the rapid evolution of viruses, their limited spectrum of activity and the time needed for a new drug to be developed. These restrictions have led to a resurgence of interest in host directed antiviral therapies as a possible alternate means of therapy. Host directed therapies involve targeting cellular pathways and immune responses in the host that viruses exploit to enter, replicate and survive. This review discusses the mechanisms of host directed antiviral strategies such as the activation of innate immune pathways using Toll like receptor and RIG I like receptor and regulation of cytokine responses, autophagy mediated viral clearance and metabolic reprogramming of infected cells. The antiviral roles of double stranded RNA molecules and their synthetic analogues, including interferon inducers like poly I:C, that promote antiviral immunity against a wide spectrum of viruses is emphasized. The review also underscores the potential of drug repurposing in getting drugs available for viral outbreaks and the diverse families of therapeutic potential of host directed therapies. Furthermore, the challenges of translation, identification of biomarkers and safety and ethics issues with these therapies are discussed. Host directed antiviral therapy is overall an effective approach that can be used in order to increase pandemic preparedness or to create effective broad spectrum antiviral drugs against future emerging viral diseases.

Keywords:

INTRODUCTION

Emerging and reemerging viruses can cause severe outbreaks in other parts of the world and can easily spread in viral infections, which remain a huge public health problem around the world. With the emergence of recent pandemics like Coronavirus Disease 2019, Ebola virus disease and influenza, the need for effective antiviral therapies that could do a fast response against newly emerging pathogens is the greatest. (Morens & Fauci, 2020; Zumla et al., 2016) Most viruses, particularly RNA viruses, tend to undergo very rapid mutation, enabling them to evade immune

systems and also becoming resistant to antiviral treatment. (De Clercq & Li, 2016; Hughes & Andersson, 2015).

Antiviral drugs are conventional and mostly attack viral proteins or mechanisms of viral replication. While these therapies can lower viral levels, they may not be broadly effective and could become less effective as viral mutation occurs continually. (Bekerman & Einav, 2015; Hayden & Shindo, 2019) Furthermore, new antiviral drugs are costly and slow to develop, and rely on traditional therapeutic strategies, which would not be able to control future pandemics quickly enough. (Mercorelli et al., 2018; Pushpakom et al., 2019)

Due to these restrictions, researchers are turning more to host directed therapies as a new approach to antiviral treatment. Host directed therapies involve attacking host cellular pathways and immune mechanisms that are utilized by viruses for replication and survival within host cells. (Kaufmann et al., 2018; Schwegmann & Brombacher, 2008).These therapies could offer far-reaching antiviral activity against several families of viruses and may offer decreased risk of developing antiviral resistance because host factors are far more stable than the viral genome. (Bekerman & Einav, 2015; Zumla et al., 2020)

There are exciting opportunities with repurposing of double stranded RNA based compounds and other host directed antiviral agents. Double stranded RNA molecules trigger innate immune responses, by binding to receptors that mediate antiviral defense mechanisms, and result in interferon production and viral replication inhibition(Kell & Gale, 2015; Takeuchi & Akira, 2009) Recent research indicates that one approach to addressing the pandemic preparedness that can be implemented before the availability of a virus specific drug could be effective would be host directed antiviral strategies, which offer broad spectrum protection against emerging viral infections. (Andersen et al., 2020; Vigant et al., 2015).

Limitations of conventional antiviral therapies

Traditional antiviral drugs interfere with the multiplication of viruses within host cells by binding to viral enzymes, structural proteins or steps in their replication. While it has proved effective for the treatment of a number of viral diseases, the specificity of drug–virus interactions and the limited applicability to new pathogens make it not an ideal solution. (De Clercq, 2019; Hayden & Shindo, 2019). A major drawback is the speed of the development of resistance to the viruses, especially RNA-viruses that have a high rate of mutations during replication. The genetic diversity allows viruses to overcome the pressure of drugs and results in lower long-term efficacy as seen in the influenza and HIV viruses. (Sanjuán & Domingo-Calap, 2016; Richman et al., 2016).

One drawback is that most antiviral medications have a very limited range of activities, and are created to target a certain virus instead of a whole family of viruses. This is a major concern when outbreaks of new viruses occur, where there is no existing therapy against the virus at the beginning of the spread of infection. (Vigant et al., 2015; Zumla et al., 2016). The process of developing antiviral drugs is also slow and costly, taking several years to research, validate in the lab and through several stages of clinical trials before approval. The delay in this process greatly limits the ability to respond quickly in the event of a pandemic or emergence of an infectious disease. (Pushpakom et al., 2019; Kupferschmidt & Cohen, 2020).

Another challenge is that many antiviral medications have the potential to be toxic and cause off-target effects due to the similarities between the process of viral replication and cellular machinery. Long term use can have a detrimental effect on organs and cause metabolic disorders. (De Clercq, 2019; Hayden & Shindo, 2019). Moreover, viral latency and persistence is a significant challenge, especially in infections like HIV and herpesviruses, in which the virus can remain latent in host cells and thus escape antiviral therapy. Complete eradication of a virus is very difficult, especially in these latent reservoirs. (Richman et al., 2016; Siliciano & Siliciano, 2018).

In general, these restrictions, and others, underscore the need for other therapeutic approaches, like host directed therapies that seek to inhibit stable pathways in the host rather than

rapidly evolving viral components, providing more general immunity against novel emerging viral infections. (Zumla et al., 2016; Kaufmann et al., 2018).

Host directed therapies

The idea of host directed therapies (HDTs) is that one should not directly target pathogens, which are rapidly mutating, but rather try to modify the pathways in cells that have to be manipulated to allow entry, multiplication and survival of these pathogens. This strategy will try to establish a less virally supportive intracellular environment and to boost host protective immune response. (Kaufmann et al., 2018; Zumla et al., 2020).

The concept of HDTs is closely related to those of host pathogen interactions that are mediated by pattern recognition receptors (PRRs) such as Toll like receptors (TLRs) and RIG I like receptors (RLRs). These receptors recognise viral nucleic acids like double stranded RNA, and initiate the downstream cell signaling to make type I interferon and inflammatory cytokines the first line of antiviral defence. (Rehwinkel & Gack, 2020; Onomoto et al., 2021). These innate immune pathways can be activated, leading to induction of antiviral genes called interferon stimulated genes (ISGs) that create an antiviral state in infected cells and the adjacent cells. These ISGs act at various steps of viral life cycle: viral entry, genome replication, protein synthesis, and virion assembly, and thus prevent the spread of viruses without specifically targeting the viral components. (Schoggins, 2019; Ivashkiv & Donlin, 2014).

Yet another aspect of the HDT framework is immune modulation – inappropriate or hyperactive immune responses are regulated to avoid damage to tissues. For serious viral infections, excessive cytokine production can result in immunopathology and the goal of an HDT is to maintain antiviral immunity along with controlled inflammatory responses, minimizing the severity of disease. (Tay et al., 2020; Zumla et al., 2020)

The other important aspect of host directed therapeutic strategy is drug repurposing. Emerging viral outbreaks can be translated rapidly into clinical practice by focusing on approved drugs with known safety profiles that have the ability to target host pathways involved in viral replication, rather than traditional drug discovery pipelines. (Pushpakom et al., 2019; Mercorelli et al., 2018).

The third layer of the conceptual framework is the employment of natural agonists of the innate immune system like double stranded RNA mimics. They can bind to cytosolic sensors such as RIGI and MDA5 to increase interferon-induced antiviral responses and thus also broad-spectrum protection against different families of viruses. (Onomoto et al., 2021; Rehwinkel & Gack, 2020).

Host directed therapies, in general, are a multi-layered conceptual therapy that combines immune activation, immune regulation, and targeting host pathways. This approach changes the paradigm from pathogen oriented therapy to host oriented intervention, and is a possible approach for future pandemics in general. (Kaufmann et al., 2018; Schoggins, 2019; Zumla et al., 2020).

Molecular Mechanisms Underlying Host-Directed Antiviral Strategies

Host-directed antiviral strategies rely on different molecular mechanisms, such as the activation of innate immunity, the regulation of cytokine responses, viral clearance by autophagy and metabolic reprogramming of host cells to inhibit viral replication and propagation (Kawai & Akira, 2011; Rehwinkel & Gack, 2020).

The innate immune system is the first line of defense against viral invasion and the recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and RIG-I-like receptors (RLRs) activates the production of type I interferon and inflammatory cytokine cascades (Kawai & Akira, 2011).

TLR3 is found on endosomal membrane of dendritic cells, fibroblasts and epithelial cells and binds viral double-stranded RNA (dsRNA). Binding of dsRNA stimulates activation of TRIF signaling pathway, which leads to activation of IRF3 and NF-kB and production of IFN-beta and pro-inflammatory cytokines. TLR3 is phosphorylated by Bruton's tyrosine kinase (BTK)

at Tyr759 that is crucial for downstream signaling (Guo et al., 2021; Matsumoto & Seya, 2011).

RIG-I-like receptors are a family consisting of three members: RIG-I, MDA5 and LGP2. RIG-I can recognize short dsRNA molecules bearing 5'-triphosphate ends, while MDA5 can recognize long dsRNA intermediates. Ligand binding releases CARD domains which engage with MAVS, leading to the formation of signaling complexes with TRAF3, TBK1 and IKKepsilon, and ultimately the production of interferon (Rehwinkel & Gack, 2020; Seth et al., 2005).

The coordinated activation of both TLR and RLR pathways is crucial for antiviral defense. Both pathways are important and work synergistically with each other in the production of interferon-beta and antiviral immunity as seen in rhinovirus and dengue virus infections (Slater et al., 2010; Nasirudeen et al., 2011).

The viruses have developed systems to inhibit PRR signaling. Jiang et al., 2021 and Mukherjee et al., 2011 showed that SARS-CoV-2 ORF9b prevents RIG-I/MDA5-MAVS pathway, TLR3-TRIF, and cGAS-STING pathway, and enteroviruses and coxsackieviruses directly cleave TRIF and MAVS proteins, therefore evading interferon responses.

Cytokine production and immunomodulatory effects

Type I interferons are crucial in antiviral immunity, but over-activation or chronic over-activation of the type I interferon pathway can lead to immunopathology and damage. While antiviral ISGs are the target of interferon signaling, it also plays a role in inflammatory lung damage in cases of severe viral infection (Ivashkiv & Donlin, 2014; Davidson et al., 2015).

High IL-6, TNF-α and low type I IFN responses have been found to be associated with severe COVID-19. The MyD88 signaling also helps to initiate inflammatory response, and MyD88 TIR domain inhibitors have been reported to decrease inflammation and enhance interferon responses (Coperchini et al., 2020; Loiarro et al., 2007). RSV inhibits interferon signaling by NS1/NS2-mediated degradation of STAT2 and favors Th2/Th17 polarization, both of which help to drive chronic airway inflammation. A range of emerging immunomodulatory therapies aimed at targeting JAK-STAT signaling pathways, inflammasomes and cytokines like IL-6 and IL-1beta, are designed to help restore immune balance (Hijano et al., 2019).

Host-directed immunotherapy involves therapies that strengthen protective immunity but reduce inflammation against pathogens such as viruses and bacteria, including cytokine, checkpoint modulation and metabolic therapies (Wallis et al., 2023). The mechanisms of viral clearance by autophagy are examined. The mechanism of viral clearance by autophagy is investigated. Lysosomal degradation is an evolutionarily conserved mechanism known as xenophagy, which also plays a role in antiviral defence by selectively targeting intracellular pathogens to be degraded (Deretic et al., 2013).

Interferon signaling through TLR3 is a major process that is dependent on the process of autophagy. Inhibition of autophagic flux has been shown to dampen antiviral responses, while TRAF6-mediated ubiquitination of Rab7 ensures that the autophagosome-lysosome fusion takes place by recruiting syntaxin 17 (Delgado et al., 2008; Zhao et al., 2023). SARS-CoV-2 Orf3a, Orf7a & NSP6 proteins block fusion of autophagosomes and lysosomes resulting in incomplete autophagy and enhanced virus persistence & inflammation. TFEB has become a key regulator of lysosomal biogenesis and autophagic flux (Miao et al., 2025). STING pathway activation by ADU-S100 improves the clearance of intracellular pathogens like Mycobacterium tuberculosis by autophagy. In addition, the modulation of autophagy in macrophages is also being explored as a pathway to eliminate intracellular pathogens, with the application of nanomaterials (Wang et al., 2024).

Viral reprogramming of glycolysis, lipid metabolism, amino acid metabolism and mitochondrial function, all of which are crucial to viral replication, is a potential therapeutic target (Thaker et al., 2019). Influenza A virus, SARS-CoV-2 and dengue virus activate the PI3K/Akt and HIF-1alpha signaling pathways to induce aerobic glycolysis in cells as a strategy for virus biosynthesis. Senexin A blocks production of the

infectious particle (Mayer et al., 2019) and the replication of dengue virus.

Some proteins are highly associated with SARS-CoV-2-induced changes in lipid metabolism including FASN, LIPA and ORMDL2. Cholesterol metabolism plays an essential role in viral entry and membrane fusion, and hence, drugs that modify the cholesterol metabolism may be potentially antiviral drugs (Yan et al., 2022). Flaviviruses use lipid droplets for replication and for energy production, including dengue and Zika viruses. Both DGA1 inhibition and statins and AMPK activators have broad-spectrum antiviral effects, with DGA1 inhibition reducing Zika virus replication and brain inflammation (Dias et al., 2023; Merino-Ramos et al., 2017).

Despite the fact that these pathways can be manipulated by viruses for immune evasion, interferon stimulated genes (ISGs) regulate pathways of glycolysis, lipid metabolism and amino acid pathways which create antiviral states. This interaction forms the virus–metabolism–IFN regulatory network (Zhang et al., 2025).

dsRNA Viruses and Synthetic Analogues

The strong pathogen-associated molecular pattern (PAMP) recognised by TLR3, RIG-I, MDA5 and PKR is double-stranded RNA (dsRNA) and this leads to the induction of antiviral states via the release of type I and type III interferon (Alexopoulou et al., 2001; Kawai and Akira, 2011). TLR3 is activated by dsRNA which triggers the TRIF-dependent pathway to produce IFN-beta, inflammatory cytokines and chemokines. dsRNA is also shown to activate the NK cells, dendritic cell maturation, and priming of cytotoxic T cells; this is why it is also used in vaccine adjuvants and antiviral therapies (Matsumoto & Seya, 2011).

Polyinosinic-polycytidylic acid (poly I:C) is a synthetic analog of double-stranded RNA (dsRNA) which can activate TLR3, MDA5 and RIG-I. It is the stabilized form of it, poly-ICLC (Hiltonol), that has been widely studied as a vaccine adjuvant and as an immunotherapeutic agent (Caskey et al., 2011). Poly I:C was administered via intranasal route to SARS-CoV-2 infected mice, which led to decreased virus load, diminished cytokine storm, enhanced infiltration of NK cells and survival. Besides, research using vaccines shows that poly-ICLC helps the production of antibodies and T-cell responses against both CD4 and CD8 cells (Bortolotti et al., 2022; Stahl-Hennig et al., 2009).

Formulations of poly I:C, such as nanoplexed formulations (BO-112), enhance the delivery of poly I:C to cells and its immunostimulatory properties. It causes immunogenic cell death and causes infiltration of T-cells through the action of IFN and is being currently investigated in cancer immunotherapy trials (Aznar et al., 2019). Oncolytic viruses selectively infect tumor cells, replicate and activate antiviral immune responses through the toll-like receptor 3 (TLR3) and RLR signaling pathways. Some clinically tested oncolytic viruses are already available, including reovirus and Talimogene laherparepvec (T-Vec) (Russell et al., 2012; Andtbacka et al., 2015). It is thought that oncolytic virus induced immunogenic cell death and the release of PAMPs and DAMPs can be used to induce activation of dendritic cells and adaptive immunity and could be adapted to create vaccines against viruses (Kroemer et al., 2013).

The pre-exposure antiviral priming is immune activation with dsRNA to establish short-term antiviral state before exposure. The concept is called superinfection therapy (SIT), which is based on viral interference mechanisms (Kovesdi & Bakacs, 2019). In human clinical trials, the antiviral activity and safety of Infectious Bursal Disease Virus (IBDV), an avian non-replicating dsRNA virus vaccine, have been demonstrated in clinical trials with hepatitis viruses, SARS-CoV-2 and herpes zoster infections (Bakacs et al. 2026).

Pandemic Preparedness

Poly I:C activation of innate lung immunity provides early immunity which could be of great benefit during initial outbreaks and could be a bridge until vaccines are rolled out. These host directed strategies align with the overall concept of an ‘one drug, multiple bugs' antiviral strategy (Kovesdi & Bakacs, 2019).

Drug Repurposing in Host-Directed Antiviral Therapy

Many viruses are reliant on the common process of the host cell for entry, replication, assembly, immune evasion, and release, making host-directed antiviral therapy an important alternative to traditional direct-acting antiviral strategies as described by Kumar et al., (2020). Host-directed antivirals work by disrupting cell pathways that are used by the virus, and are therefore not directed against a viral protein, as are the virus-targeted drugs (Bolinger et al., 2024). This could be useful for rapidly emerged viral infections, where there are no drugs already available to attack the virus in question. Host Directed Therapy has become a hot topic again during the COVID-19 pandemic as SARS-CoV-2 as an RNA virus heavily depends on host receptors, proteases, endosomal trafficking, lipid metabolism and inflammatory signaling pathways and immune-regulatory pathways. Thus, the concept of drug repositioning in the field of host-based antiviral agents offers an operational roadmap for finding existing drugs which could be quickly tested against novel viral pathogens (Chakraborty et al., 2021).

Drug Repurposing is particularly important for drug discovery in public health emergencies, as it can save time, costs, and uncertainty involved in de novo drug discovery, Gatti et al. (2021) explain. Typically need years of target validation, compound screening, toxicity testing, and staggered clinical trials to develop an antiviral (Garcia-Blanco et al., 2022). By contrast, the pharmacokinetic, pharmacodynamic, manufacturing, dose and safety profiles of repurposed FDA-approved or EMA-approved drugs are known (Du et al., 2026). However, this does not mean that repurposed drugs could be used without new evidence, it does mean that the obstacles to early toxicology and formulation are reduced. This advantage is even greater in the concept of host-directed antiviral therapy, where many potential drugs are already in development for cancer, inflammatory diseases, autoimmune disorders and metabolic diseases and infectious diseases, but that interfere with cell pathways that are also targeted by viruses (Gatti et al., 2021).

As drug repositioning of regulatory-agency approved drugs and investigational compounds with known safety can significantly speed up the process of developing a new antiviral drug compared to identifying new compounds, Smith et al. (2022) report that this approach holds great promise. The acceleration is especially significant for epidemic and pandemic situations where there is an urgent clinical need and for healthcare systems are under intense strain (Ginex et al., 2021).

Another positive about the FDA approved drugs shot at being repurposed is that researchers can leverage available data on drug–drug interactions, contraindications, dosage levels, dosage rates and adverse reactions. The literature, however, also points to the fact that, for one disease, the drug may indeed be safe, and can be effective for a second disease, even if the dosage is the same and the population identical, and even if the drug is used during acute viral illness. Thus, the benefit of FDA approved repositioning is not avoiding clinical evaluation, but rather is the acceleration, evidence-based, and ease of clinical evaluation in times of emergency (Greenblatt et al., 2023).

Host-targeting repurposed drugs are given by Ginex et al. (2021), who identified FDA-approved drugs that could disrupt the host entry related mechanisms utilized by SARS-CoV-2 like cepharantine, clofazimine, metergoline, imatinib, and efloxate (Karim et al., 2023). As demonstrated in these examples, host-directed repurposing is applicable not only for classical antivirals but also for other drugs developed for different therapeutic indications, which could potentially affect the process of virus entry, membrane fusion and endosomal transport, kinase signaling, or inflammatory pathways (Kumar et al., 2020). For instance, host kinases have been shown to control viral cell entry and trafficking inside the cell and have been the target of study, such as the use of imatinib (Low et al., 2025).

In the same way, immunomodulatory agents have been tested as they may be necessary to prevent dysregulated host inflammation to which severe viral disease may be a consequence. As illustrated by these examples, host-directed repurposing can broaden the scope of viral envelope protein

and/or viral enzymes to include antivirals targeting other host proteins and enzymes (Mercorelli et al., 2025).

According to Chakraborty et al. (2021), COVID-19 provided one of the largest real-world venue platforms to test antiviral drugs—including large simultaneous platform trials like RECOVERY and ACTT which tested several drugs at once. It was also noted that the evidence gained from these trials highlighted an important finding: repurposing can be beneficial, but not if not validated properly in clinical trials (Smith et al., 2022). Several treatments that demonstrated encouraging efficacy in laboratory or observational trials have not proven to have a significant impact in clinical RCTs. Other modalities of immunomodulation demonstrated improvement in certain groups of patients in particular, especially if disease severity required suppression of excessive inflammatory responses. This is key for host-directed antiviral therapy as time and patient selection are important factors (Tran et al., 2021). One therapeutic option that could be toxic is a host-directed drug that is given too early, too late, or to patients with an absence of activation of inflammatory pathways or cellular pathways (Schloer et al., 2022).

Broad-Spectrum Potential against Diverse Viral Families

Karim et al., (2023) make the case that we should be ready for new viruses with broad-spectrum antiviral drugs as well; because of their delay in becoming available, they can't be prepared for in time when a new virus arises. Broad spectrum strategy: aiming for conserved viral functions, or conserved host pathway(s) common to many viruses (Cakir et al., 2021). These host-directed antivirals are particularly appealing in this setting since multiple viruses might require the use of host proteins and enzymes, including cellular receptors, proteases, lipid metabolism, nucleoside synthesis, endosomal acidification, autophagy, innate immune signaling, or translation machinery. This mutual reliance gives the opportunity to seek treatments that are not specific to one virus but could prove helpful to many in different viral groups. Hence, host-directed drug repurposing helps to foster the bigger plan for pandemic preparedness, which involves creating drug libraries for use before the next pandemic (Kumar et al., 2020).

Due to their high mutation rate, recombinative ability, ecological adaptability, and zoonotic transmission, RNA viruses are considered by Garcia-Blanco et al. (2022) as one of the most important causes of emerging/re-emerging infectious diseases. Influenza viruses, coronaviruses, filoviruses, flaviviruses, arenaviruses, paramyxoviruses and alphaviruses have repeatedly proven to be of pandemic or epidemic potential (Xie et al., 2022). In this scenario, broad-spectrum host-directed therapies could offer significant protection as many types of RNA viruses share similar requirements for replication, and many fall into a category that is not a target for conventional antivirals. Examples are the requirement for host nucleotide pools, membrane remodeling, innate immune suppression, protein translation systems, and intracellular trafficking by RNA viruses. These shared factors could also be targets for designing a new kind of antiviral drug that could be used for multiple emerging RNA viruses (Wei et al., 2021). The study by Mercorelli et al. (2025) indicates that there is a growing interest in repurposing of antiviral drugs, ranging from experimental methods like molecular docking, omics-based target discovery, phenotypic screening, and network pharmacology to artificial intelligence-driven predictions. Such methods would be especially useful for finding drugs that will act as a broad-spectrum antiviral agent since they would be able to find agents that disrupt pathways that the cell uses during viral infection (Pires et al., 2021). The screening of antifungal, anticancer, antimalarial, anti-inflammatory and metabolic drugs for antiviral activity is an example, since some of the mechanisms of action may overlap with viral dependency pathways. Thus, the value of repurposing extends beyond the possibility of emergency use of old drugs, it also contrasts the possibilities of systematically investigating drug-host-virus interactions to look for new therapeutic strategies that could be applied across viral families (Tang et al., 2025).

The findings in the study of coronavirus specific antivirals highlight the need for broad spectrum, virus-specific and host-directed therapeutics in preparation for future outbreaks, Bolinger et al. (2024) state. Coronaviruses are a useful model due to their different replication mechanisms, but also for their differences in transmissibility, pathogenicity and in patterns of immune response to SARS-CoV (2002), MERS-CoV (2012) and SARS-CoV-2 (2019). This could result in the emergence of viral targets resistant to a narrow antiviral compound and or the inapplicability of a given compound against a specific virus. On the other hand, the literature also warns of the need for broad-spectrum activity to be balanced by safety due to the potential to alter normal cellular activity in a host-targeted drug. A model best suited to pandemic preparedness is thus broad-spectrum screening, coupled with rapid clinical trial platforms, and genetic surveillance, with adaptive regulation (Gholap et al., 2025).

Low et al. (2025) also point out a potential for repurposing of host-directed antivirals, because many drugs already approved by the FDA or EMA have an impact on pathways that are relevant for virus entry, replication, or immune regulatory mechanisms that can be crucial in the context of circulating and emerging viruses. This is especially critical for newly emerging zoonotic viruses, where there is either a low level of immunity or none in man, and no specific pathogen treatments are available (de Siqueira Santos et al., 2025). Zoonotic viruses frequently emerge to infect a new species, for which there is no opportunity to the traditional drug development process. If that is the case, the broad-spectrum repurposed drugs may provide bridge therapeutics until effective vaccines, mAbs, and specific antivirals are available (Xavier V & Ravichandran, 2025). However, the term broad-spectrum potential isn't a translation of “universal. The existing host-directed drug may inhibit a host pathway that is important to one family of viruses but not to another. Thus, it is necessary for a broad-spectrum therapy not only to have observation but also to have strong evidence in the machine mechanism of the antiviral action.

Ethical Considerations

While there are obvious benefits to host-targeted antiviral therapy, direct-acting antivirals are frequently relatively well tolerated due to their lack of use of human cellular pathways as targets, as explained by Matsunaga et al. (2026). One of the primary issues with host-directed therapy is the fundamental fact that the same pathway that a virus reactivates will also serve some normal function for the host (Bolinger et al., 2024). Thus, adverse effects of immune modulation, kinase inhibition, metabolic interference, or translation control can occur. Safety is particularly complicated in cases of acute viral infection where the host is already in morpho-functional stress of inflammatory, metabolic and immunobiological nature. What is safe for long term use in the context of one disease may not be safe in an acutely infected patient, elderly, pregnant, immunocompromised patients or patients with multiple comorbid diseases (Chakraborty et al., 2021).

One of the major associated risks highlighted by Kumar et al. (2020) lies in immune over activation, which is a result of manipulating host antiviral responses. Host-directed therapy might try to boost natural immunity, block inflammatory cytokines, block immune checkpoints or regulate anti-viral signaling processes (Du et al., 2026). But, the equation of outcome of viral disease depends on an intricate balance between clearance of these viruses and damage to tissues secondary to immune response (Garcia-Blanco et al., 2022). Immune stimulating therapies, if not used properly, may exacerbate inflammatory response, promote cytokine-mediated damage or exacerbate vascular, respiratory, hepatic or neurological complications. On the other hand, over-immune suppression can hinder elimination of the virus and provoke the threat of secondary infections. Thus, the timing of the use, dosage of host-directed antiviral therapy as well as the selection of biomarker and stratification of patients is significant (Gatti et al., 2021).

Gatti et al. (2021) mention the main regulatory and ethical issues related to drug repurposing activities during the COVID-19 pandemic, especially for the promotion of several drugs

without supporting evidence. This is one of the key points to note about host-directed therapy as some repurposed immunomodulators or pathway inhibitors may lead to major side effects if used outside of clinical trials (Ginex et al., 2021). Issues of ethics come into question concerning the use for purposes other than those approved by the regulatory body in obtaining approval for trials when emergencies arise and, as a result, less-than-adequate informed consent remains unobtained, monitoring or trials remain incomplete. Approved drugs should not be assumed to be safe when repurposed (Greenblatt et al., 2023). Approval applies only to the specific disease and may be different if applied to other diseases, stages of disease, or being used in combination with other antivirals, supportive care or corticosteroids, or anticoagulants (Karim et al., 2023).

Emergency Use Authorization can help to facilitate quick access to therapy during critical times, but only works in conjunction with robust transparency, evidence standards, and post-authorization monitoring, according to Tran et al. (2021). The problem is that decisions about emergencies are usually made with uncertainty, which poses an ethical challenge (Kumar et al., 2020). In the case of host-directed repurposed drugs, such uncertainty can encompass incomplete understanding of long-term effects on immunity, disease-specific risks, and optimal dosing among different populations and with regard to disease. Monitoring after authorization is thus necessary to detect rare adverse events, as well as to rescind or revise particular authorizations, when new information emerges that alters the understanding of the benefit–risk balance. This was evident during the COVID-19 time of several emergency authorizations being amended, restricted and withdrawn with changing variants and emerging data (Low et al., 2025).

Another key limitation is the ability to modulate host pathways over long periods of time (Du et al., (2026). Most antiviral therapies are short term, but some host-directed therapies could impact on inflammation, cell survival, metabolism and immune memory. If these are repeatedly changed or changed for a prolonged duration there can be potential risks such as immune regulation or delayed healing or disturbances in metabolism, or increased susceptibility to other infections (Mercorelli et al., 2025). Theoretical significance of autoimmunity risk also has been placed on some models of host-directed interventions that target changes in the cytokine network, interferon responses, antigen presentation or lymphocyte activation. Not all host-directed drugs have the same risk of causing or exacerbating autoimmune phenomena, but rigorous clinical-trial exclusion criteria, adverse-event surveillance and follow-up is needed (Smith et al., 2022).

With respect to clinical trials, Chakraborty et al. (2021) demonstrate that the trials were riddled with difficulties during COVID-19 drug-repurposing attempts. A number of these early studies were either small, under-powered, non-randomized or with their varying endpoints not consistent. Some trials included patients at different stages of the disease and it is hard to tell if a treatment failed to help patients because it was ineffective or occurred at an incorrect stage of the disease. Host directed antiviral trials are complicated further by the fact that these trials may depend on inflammatory markers, viral load, immune status, comorbidities or background treatment (Tran et al., 2021). As examples, a hyper inflammation blocking drug could be useful for hospitalized patients but not in mild outpatient patients; an immune stimulating drug might help early in inflammatory disease but could worsen the disease in severely affected people. Hence, adaptive platform trials, biomarker enrollment and standardized endpoints are crucial in assessing host-directed repurposed antivirals (Schloer et al., 2022).

Greenblatt et al., (2023), suggest that the effectiveness of these trial investigations relied on the designs, coordination and quality of evidence provided during the COVID-19 pandemic as vast trial investigating efforts occurred. This discovery has ethical consequences as the existence of such poorly-designed trials might put some subjects at risk without any beneficial knowledge gained. During a pandemic, small trials might also be competing for participants and resources, thus adding to the delay in finding answers (Kumar et al., 2020). But with host-directed repurposed

drugs, there is a demand for scientifically justified dosing, careful and regular safety monitoring, ethical clinical research necessitating equipoise, and the swift dissemination of data. It also involves not exaggerating claims in the public arena prior to trial times (Xie et al., 2022). The literature thus argues for a model which looks to the evaluation of repurposed host-directed therapies in a coordinated national or international system instead of in disjointed, poorly powered studies (Cakir et al., 2021).

Translational Challenges and Clinical Implementation

Host directed therapies (HDTs) are a class of therapeutics derived from the laboratory to clinical practice that are difficult to implement because of host pathogen interactions and the different responses of hosts. While targeted to conserved host pathways, implementation of HDTs in clinics is hampered by the lack of understanding of which host factors can be modulated without adversely affecting the host system. (Kaufmann et al., 2018; Zumla et al., 2020).

One of the critical translation barriers is the absence of reliable and validated biomarkers to predict therapeutic response and disease progression while receiving antiviral therapy. Many viruses have variable immune responses in humans, which makes it challenging to find common markers that accurately represent the effectiveness of therapy or clearance of virus. (Ng et al., 2021; Schoggins, 2019).

Recent studies highlight the need to include immunological and molecular markers such as interferon stimulated gene signatures, cytokine profiles, and host gene expression patterns in successful clinical implementation of HDTs. These are critical for patient stratifications, treatment response monitoring and reduction of risk of immune over activation/immune suppression during treatment. (Ivashkiv & Donlin, 2014; Tay et al., 2020).

One of the challenges for translation is the complexity of the host signaling networks targeted by HDTs. Host pathways are all interconnected, therefore, when a pathway is targeted for a therapeutic intervention, additional pathways may also be affected, and off target effects may occur. This complexity has led to the need to optimize the dose and safety evaluation during clinical development. (Rehwinkel & Gack, 2020; Onomoto et al., 2021).

The lack of strong preclinical models to recapitulate human viral infections also places a constraint on clinical implementation. Numerous candidate antiviral agents that are potent in cell culture have not been effective in humans because of differences in the functions of the human immune system and human genetic variations. Preclinical data is not directly translated to clinical results, which leads to a lag time. (Shepherd et al., 2025; Kaufmann et al., 2018).

Moreover, the emergence of antiviral strategies based on biomarkers is still in its early phases and a common platform for diagnosis of HDT monitoring is lacking. New technologies in systems biology and high throughput omics are now being investigated to find predictive biomarkers that could be used to inform personalized antiviral therapy and enhance clinical trial design. (Ng et al., 2021; Pushpakom et al., 2019; Schoggins, 2019).

In general, the translating success in host directed antiviral therapy is dependent on the identification of well-established, reproducible and clinically validated biomarkers. These biomarkers will play a crucial role in moving from basic research to clinical use to allow for safe and effective implementation of antiviral strategies that will impact the entire spectrum of the pandemic in future preparedness. (Zumla et al., 2020; Shepherd et al., 2025; Kaufmann et al., 2018).

Future Directions

With the emergence of new viral outbreaks, new antiviral strategies are moving away from pathogen-specific drugs towards broad-spectrum and host-directed drugs that can deliver quick responses. The need for ready-to-go approaches with scalable and quickly available therapeutics that can target multiple viral families was highlighted during the COVID-19 pandemic. (Thom & D'Elia, 2024; Du et al., 2026).

The discovery and attack of conserved host factors that are commonly used by various viruses to gain entry into the cell and replicate, as well as to evade the immune response, is another promising future strategy. These strategies target host pathways, not viral proteins, so they minimize chances of resistance formation and offer greater coverage of the antiviral world against future unknown viruses. (Kaufmann et al., 2018; Wallis et al., 2023).

A major improvement is the application of high throughput screening technologies like CRISPR-Cas systems, RNA interference and multi-omics technologies for a rapid identification of host dependency factors and potential therapeutic targets. It is hoped that these will greatly speed up the discovery of antiviral drugs and help equip the world for the next pandemic. (Thom & D'Elia, 2024; Du et al., 2026).

The use of pre-existing drugs with established safety profiles to rapidly test new pathogens, such as those emerging during a pandemic, is also another important aspect of pandemic-ready therapeutics the process of drug repurposing. This is a substantial reduction of the time required for drug development when compared to the traditional drug discovery programs and has been relevant during the recent outbreaks worldwide. (Pushpakom et al., 2019; Sanders et al., 2020)

Moreover, development of broad-spectrum antivirals (BSAs) and combination therapies are becoming a focus of interest as a means to attack multiple stages of a viral life cycle. These can improve the effectiveness of the treatment and minimize the chance for escape mutations of viruses during treatment. (Vigant et al., 2015; Zhu et al., 2015).

Predictive modelling and surveillance systems that encompass the evolution of viruses, risk of zoonotic spillover and host immune responsiveness on a global scale are another critical piece expected in the future. These systems may be useful for early detection of pandemic threats and accelerate therapeutic development strategies (Morens et al., 2021; Du et al., 2026).

In conclusion, the development of pandemic-ready therapeutics will depend on an integrated approach that involves host-directed therapies, fast drug repurposing, broad-spectrum antiviral development and advanced genomic technologies to be prepared for future outbreaks of viral diseases. (Kaufmann et al., 2018; Thom & D'Elia, 2024; Wallis et al., 2023).

Conclusion

Host directed antiviral therapies are a new and promising way to fight emerging and reemerging viral infections. Host directed therapies target stable pathways and immune mechanisms within the host cell that are necessary for viral replication and survival, while traditional antiviral therapies generally target viral proteins and are often rendered ineffective by the rapid mutations that occur in the virus. This could provide wide range antiviral activity and minimize antiviral resistance. The central molecular mechanisms of host directed antiviral strategies that were identified in this review were activation of innate immune system via Toll like receptors and RIG I like receptors, cytokine regulation, viral clearance mediated by autophagy and metabolic reprogramming of infected cells. Possible antiviral effects of double stranded RNA molecules and synthetic analogues like poly I:C were also discussed as these molecules have been found to be stimulatory of interferon production and enhance antiviral immunity. Moreover, the review highlighted that drug repurposing is an emerging and rapid tool to identify antiviral drugs in the outbreak and pandemic scenario at low cost.

There are a number of issues that have hindered the clinical use of host directed therapies so far: toxicity, immune over activation, and the absence of reliable biomarkers and the challenges of moving experiments to the clinic. Thus, careful clinical evaluation, patient-specific biomarker identification and long term safety monitoring are vital for the successful implementation. Overall, host directed antiviral therapies offer a promising baseline for future therapeutics that are pandemic ready and potentially offer significant support in terms of the development of safer and more effective broad spectrum antiviral therapies.

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