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## Host directed therapies: COVID-19 and beyond

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### ARTICLE INFO

#### Keywords:

Host directed therapy  
Human coronavirus  
SARS-CoV-2  
COVID-19

### ABSTRACT

The global spread of SARS-CoV-2 has necessitated the development of novel, safe and effective therapeutic agents against this virus to stop the pandemic, however the development of novel antivirals may take years, hence, the best alternative available, is to repurpose the existing antiviral drugs with known safety profile in humans. After more than one year into this pandemic, global efforts have yielded the fruits and with the launch of many vaccines in the market, the world is inching towards the end of this pandemic, nonetheless, future pandemics of this magnitude or even greater cannot be denied. The preparedness against viruses of unknown origin should be maintained and the broad-spectrum antivirals with activity against range of viruses should be developed to curb future viral pandemics. The majority of antivirals developed till date are pathogen specific agents, which target critical viral pathways and lack broad spectrum activity required to target wide range of viruses. The surge in drug resistance among pathogens has rendered a compelling need to shift our focus towards host directed factors in the treatment of infectious diseases. This gains special relevance in the case of viral infections, where the pathogen encodes a handful of genes and predominantly depends on host factors for their propagation and persistence. Therefore, future antiviral drug development should focus more on targeting molecules of host pathways that are often hijacked by many viruses. Such cellular proteins of host pathways offer attractive targets for the development of broad-spectrum anticipatory antivirals. In the present article, we have reviewed the host directed therapies (HDTs) effective against viral infections with a special focus on COVID-19. This article also discusses the strategies involved in identifying novel host targets and subsequent development of broad spectrum HDTs.

### 1. Introduction

The global spread of “severe acute respiratory syndrome coronavirus-2” (SARS-CoV-2), the causative agent of COVID-19 pandemic, which originated in Wuhan, China in December 2019, is still ongoing and causing enormous loss of lives, strict lockdowns in several parts of the worlds, closing down of businesses and loss of employments around the globe (Gupta, 2020; Meganck and Baric, 2021). Globally 179,686,071 individuals tested positive for SARS-CoV-2, and 3,899,172 succumbed to the disease as on June 25, 2021 (<https://covid19.who.int/>).

Despite facing two corona virus outbreaks, i.e. severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS) and several other viral outbreaks and epidemics like Dengue, Chikungunya, Zika and Ebola in the 21st century, the world was clueless and totally unprepared for COVID-19, with not even a single therapeutic option available to tackle the pandemic. Moreover, developing a safe and

effective drug from scratch was an impractical idea as the average time frame from start to the approval stage for any new drug is 12 years, hence the scientific community focused their efforts on the repurposing of approved drugs, that yielded minor success with approval of remdesivir and dexamethasone (DiMasi et al., 2016).

The most important lesson learnt in the COVID-19 pandemic, is to act proactively against future viral pathogens instead of reacting to the novel viruses as they emerge. The actions include anticipation and accurate prediction of future pandemics based on the available resources, followed by preparation to minimize the harmful effects by developing broad-spectrum antiviral drugs, vaccines and other therapeutic modalities.

Past two decades have witnessed approximately 10 viral epidemics or pandemics caused by the members of coronavirus, myxovirus, alphavirus, filovirus and flavivirus family in addition to other sporadic outbreaks of henipaviruses, arenaviruses, bunyaviruses, and other RNA viruses

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<https://doi.org/10.1016/j.crphar.2021.100058>

Received 29 June 2021; Received in revised form 14 September 2021; Accepted 19 September 2021

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(Meganck and Baric, 2021). Moreover, zoonotic viruses, which occasionally spill over in various animals, serve as a reservoir host for these viruses and constitute a serious threat for spread in humans. Thus, identifying these viral threats circulating in animal reservoirs is the only available tool to predict future viral epidemics or pandemics (Edwards et al., 2020; Menachery et al., 2015).

The conventional methodology to battle viral infections, is to develop effective antiviral drugs and this approach has been successful in the development of antiviral therapeutics against herpes simplex virus (HSV), human immunodeficiency virus type 1 (HIV-1) and hepatitis C virus (HCV) (Cunningham et al., 2019; De Clercq and Li, 2016; Ingiliz et al., 2020), nonetheless, entire world is still waiting for effective and safe antiviral drugs against COVID-19. Most of the Food and Drug Administration (FDA) approved antiviral agents target viral encoded factors and these drugs are called as directly acting antivirals (DAA), however, the activity spectrum of these antivirals is not as broad as antibiotics and these drugs work against the selective family of viruses (Chaudhuri et al., 2018). In most cases, loss of efficacy of antivirals due to the emergence of drug resistance is another reason for concern, which necessitates exploring alternative treatment strategies for viral infections. In general, host-pathogen interactions are established only when there is an equilibrium between the host and the pathogen, and as a result of this, the pathogen survives inside the host without causing any harm. Interestingly, whether the microbe will be contained or will it lead to disease progression, depends on the intricate balance between the pathogen and host's immune surveillance mechanisms (Zumla et al., 2016).

In the past decade, an alternative strategy focusing on the development of antivirals targeting host factors termed as host directed therapy (HDT) has gained momentum. HDTs augment the host defence mechanisms by improving the immune response to pathogens by targeting the virulence factors and modulating the disease related inflammation leading to better clinical outcomes such as reduced organ damage, mortality and morbidity (van de Wakker et al., 2017; Zumla et al., 2020). Unlike conventional DAAs, HDTs are primarily impervious to drug resistance as the host factors or pathways are critical for the survival of viruses, evolutionarily conserved and regulated by multiple genes, hence multiple mutations would be required in the pathogen for successful evasion (Kaufmann et al., 2018).

In order to successfully combat any future COVID-19 like pandemic, we should aim to develop broad-spectrum drugs effective against viruses from multiple families. The pre-emptive drugs against unknown viruses should have their phase 1 trials completed, indicating its safety for human use. In case of emergence of any epidemic/pandemic, these drugs can be included into phase 2/3 clinical trials immediately to evaluate their efficacy against the causative virus. Despite being an enormous task, it is worth pursuing, considering the catastrophe it may cause in the absence of any drug. Having drugs with their safety data, offers the advantage for rapid deployment, if the need arises. Since directly acting antivirals are family specific and have inherent risk of drug resistance, we would like to make a case for shifting our focus on HDTs due to their broad specificity and fewer chances of drug resistance. This review discusses about the current use of HDTs in viral infection, with a specific focus on COVID-19. Further, we discuss the strategies to discover and develop new HDT agents and the challenges involved in this process.

## 2. HDTs in viral diseases

All viruses are obligate intracellular parasites that require host cellular machinery and energy source to complete their life cycle. Viruses exhibit host tropism and cannot replicate outside the host. Upon infection, the host's intrinsic defence mechanisms are activated and viruses interact with hundreds of host proteins to avoid the immune responses directed against them and further hijack the host pathways. Each step of the viral life cycle utilises host factors, therefore these stages of viral life cycle also offer a potential opportunity for the development of host

directed antiviral therapeutics (Ryu, 2017). Identifying the crucial interactions between the host and the virus required for viral entry, replication, assembly and release, are the main steps towards developing novel HDTs (Kaufmann et al., 2018). Viruses utilize various aspects of epigenetic machinery to ensure the establishment of infection, spread, and persistence. Moreover, host genes involved in cell cycle progression, senescence, survival, inflammation and immunity are prime targets for such epigenetic control by viruses. Such virus mediated epigenetic modifications in the host genes constitute attractive targets for the development of HDTs. Further, viruses have devised several ways to manipulate or modify the cell processes for the evasion of immune response elicited from host immune system and restoration of perturbed immune responses by HDTs offers a great strategy in the management of viral diseases (Paschos and Allday, 2010). With technological advancements in the past two decades, our knowledge about host virus interactions has improved immensely and fueled the discovery of novel HDTs. However, most of the studies are still under various phases of clinical development with few compounds having FDA approval. Therefore, potential HDTs, which have shown antiviral effects in animal models or in clinical trials are included in Table 1 whereas compounds with only *in vitro* data are largely omitted with few exceptions such as kinase inhibitors, which are already approved for other diseases.

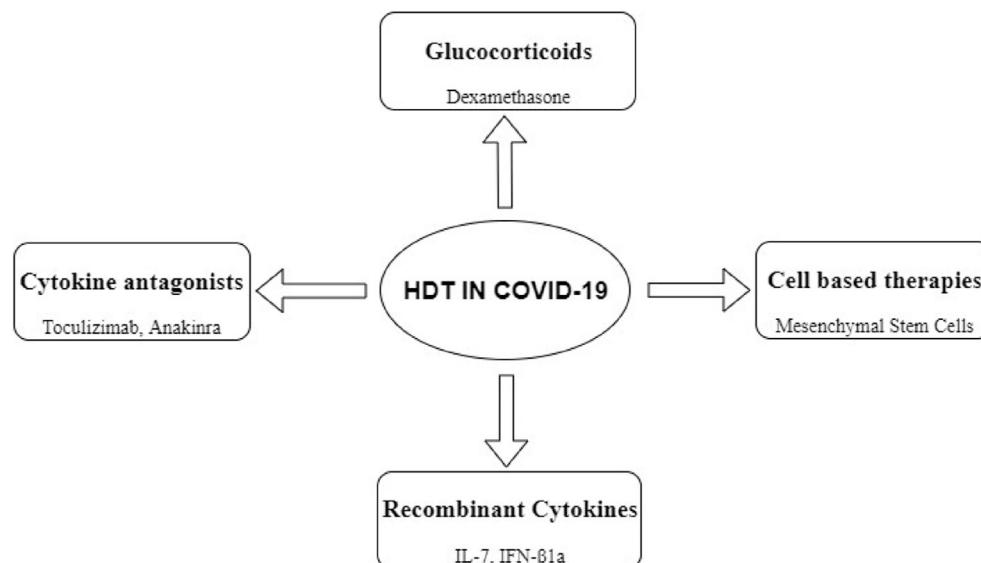
**Abbreviations** SA (Sialic acid), CCR5 (C-C chemokine receptor type 5), NTCP (sodium taurocholate co-transporting polypeptide), NPC1L1 (Niemann-Pick C1-like 1 cholesterol absorption receptor), SINE (Selective Inhibitor of Nuclear Export), CRM1 (Chromosomal Maintenance 1), XPO1 (Exportin 1), NEP (Nuclear export protein), eIF4A (Eukaryotic initiation factor 4A), CypA, (cyclophilin A), EGFR (Epidermal growth factor receptor), AAK1 (AP2 associated kinase 1), GAK (cyclin G-associated kinase), PDK1 (Phosphoinositide Dependent Protein Kinase 1), PI3K (Phosphoinositide 3-kinase), AKT (Protein kinase B, PKB), MEK (Mitogen-activated protein kinase kinase), Raf (Rapidly Accelerated Fibrosarcoma), ERK (Extracellular signal-regulated kinases), HDAC3 (Histone Deacetylase 3), Apo-A1 (Apolipoprotein A1), LEAP-1 (liver-expressed antimicrobial peptide 1), HAT (Histone Acetyltransferase); IV (Influenza Virus), IAV (Influenza A Virus), IBV (Influenza B Virus), PIV (Para Influenza Virus), HIV-1 (Human Immunodeficiency Virus-1) HBV (Hepatitis B Virus), HCV (Hepatitis C Virus), HDV (Hepatitis D Virus), HEV (Hepatitis E Virus), DENV (Dengue Virus), HSV-1 (Herpes Simplex Virus-1), CHIKV (Chikungunya Virus), ZIKV (Zika Virus) EBV (Ebola Virus).

## 3. HDTs in COVID-19

SARS-CoV-2 infection is characterized by the induction of unusual and extreme host immune responses leading to lung damage. In a small fraction of the COVID-19 patients, the aberrant activation of immune responses may lead to the huge production of inflammatory cytokines such as IL-6, TNF- $\alpha$ , IL-7, IFN- $\gamma$ , IP-10 and MCP-1, which is also called as cytokine storm. (Azhar et al., 2019; Huang et al., 2020; Hui and Zumla, 2019). Patients with cytokine storm may develop acute respiratory distress syndrome (ARDS) and consequent lung fibrosis, chronic lung damage and reduced pulmonary function if they survive the intensive care (Batawi et al., 2019; Ngai et al., 2010). Aberrant induction of immune responses in severe COVID-19 patients suggests the role of immune system based HDT interventions in the treatment of such patients. In the absence of any specific therapy for the treatment of COVID-19, existing HDTs with a different mechanism of action have played an important role in the management of COVID-19 (Fig. 1). Efficacy of HDTs depends on the timing of treatment as progression of disease severity is linked with dynamic inflammatory responses. HDTs might help in restoring the immune response, reducing the pulmonary damage, ARDS and survival benefits in COVID-19 patients.

**Table-1**  
HDTs against viral diseases.

Drug	Host Factor	Mechanism	Viruses	Ref.
Fludase (DAS181)	SA	Cleaves SA on the cell surface of host to prevent viral entry	IV, PIV	Zenilman et al. (2015)
Maraviroc (MVC)	CCR5	A CCR5-antagonist, binds to CCR5 and blocks viral entry	HIV-1	Woollard and Kanmogne (2015)
Myrcludex B	NTCP	Binds to NTCP to block the viral entry into liver cells	HBV, HDV	Bogomolov et al. (2016)
Ezetimibe	NPC1L1	Blocks viral entry by binding to NPC1L1	HCV	(Feld et al., 2020; Monrroy et al., 2017)
Aprotinin	Endosomes	A serine protease inhibitor, inhibition of viral protease activity during viral entry and endosome fusion	IAV, IBV, SARS-CoV-2	(Bojkova et al., 2020a; Song et al., 2021b)
Niclosamide	Endosomes	A category B anthelmintic drug approved by FDA, targets acidic vacuoles, endosomes and interferes with membrane fusions. Also inhibits viral RNA replication and viral maturation	SARS-CoV-2	(Backer et al., 2021; Jung et al., 2019)
Emetine	Lysosomes	FDA approved drug for amebiasis, accumulates into the lysosomes, alters the pH to impair the intracellular traffic and inhibits autophagy to hinder the autophagy mediated viral infection, accumulation of emetine in lysosomes also limits free cholesterol availability for viral assembly	ZIKV, EBV	Yang et al. (2018)
Selective Inhibitor of Nuclear Export (SINE) Compound	Nuclear export	A slow-reversible inhibitor of Exportin 1 (CRM1/XPO1), inhibits interaction between NEP and exportin-1 (XPO1) to prevent nuclear export in vRNP.	HIV-1, IV	(Boons et al., 2015; Perwitasari et al., 2014)
Verdinexor (KPT-185)	Translation	Inhibits eIF4A-dependent viral mRNA translation.	HEV	(Henss et al., 2018; Todt et al., 2018)
Silvestrol	Replication	Suppresses the synthesis and accumulation of viral RNA.	CHIKV	Pitts et al. (2017)
N-(4-hydroxyphenyl) retinamide (fenretinide or 4-HPR)	Replication	CypA antagonist, sequesters CypA and inhibits replication.	ZIKV	
Alisporivir	Replication	CypA antagonist, sequesters CypA and inhibits replication.	HCV, Flavivirus	(Fischer et al., 2010; Qing et al., 2009)
Miravirsin	Replication	miR-122 antagonist, inhibits the replication of HCV RNA and exhibits dose dependent decrease in HCV load in liver cells.	HCV	(Janssen et al., 2013; Lanford et al., 2010)
Iminosugar	Protein glycosylation	Impairs the viral protein glycosylation by inhibition of alpha glycosidase I and II.	IAV, IBV, DENV	Warfield et al. (2016b)
Uv4B	Translation	Inhibits the mRNA translation by antagonising the phosphorylation level of eukaryotic initiation factor 4E (p-eIF4E).	HSV-1	Dong et al. (2018)
Homoharringtonine (HHT)	Translation	Inhibits the mRNA translation by antagonising the phosphorylation level of eukaryotic initiation factor 4E (p-eIF4E).		
Thapsigargin	ER, Ca <sup>2+</sup> ATPase pump	An inhibitor of ER Ca <sup>2+</sup> ATPase pump, blocks IAV virus production by inducing an extended antiviral state, activates type I/III interferon response.	IAV	Goulding and Yang (2020)
Gefitinib (Iressa)	EGFR	EGFR inhibitor, Inhibits EGFR mediated signaling to block the spread of Poxvirus, Inhibits replication of HBV through down regulation of phosphorylation of STAT3.	Pox virus	(Gan et al., 2020; Langhammer et al., 2011)
sunitinib/erlotinib	AAK1 and GAK,	Inhibitors of AAK1 and GAK, perturbs AAK1 and GAK dependent intracellular trafficking viral particles which is crucial for viral infection.	HBV	Bekerman et al. (2017)
OSU-03012	PDK-1	Inhibitor PDK-1, Suppresses ZIKV replication by down regulating the PI3K/ Akt pathway.	HCV, DENV, EBV	Chan et al. (2018)
Trametinib	MEK	MEK inhibitor, Export of viral ribonucleoproteins (vRNPs) is dependent on Raf/MEK/ERK signaling cascade and inhibition of this signaling suppresses viral replication.	ZIKV	Schröder et al. (2018)
RGFP966	HDAC3	HDAC3 Inhibitor, suppresses HCV replication by regulation of Apo-A1 and LEAP-1expression.	IAV	Zhou et al. (2018)
C646	HAT	Inhibitor of HATs, improves survival of host by modulation of expression of inflammatory genes governed by HATs	HCV	Zhao et al. (2015).

**Fig. 1.** Host directed therapies used in the treatment of COVID-19.

### 3.1. Recombinant cytokines

**SNG001 (IFN- $\beta$ 1a):** In case of novel viral infections, the host lacks adaptive immunity and innate immune responses are critical for eradication of invading virus and preventing the severity of the disease. In the given scenario, interferons (IFN) play a crucial role in the maintenance of antiviral state of the host (Li et al., 2018). A recent study reported the decreased IFN response in severe COVID-19 patients (Hadjadj and Yatim, 2020). Monk et al evaluated the effectiveness of inhaled IFN- $\beta$ 1a (SNG001) in 101 hospitalised COVID-19 patients in a double blind randomised phase 2 clinical trial. SNG001 was found to be safe in patients and clinical improvement and recovery was significantly better than the placebo control group (NCT04385095) (Monk et al., 2021).

**IL-7:** Lymphopenia, a reduction in lymphocyte count, is a prominent and near uniform clinical feature in COVID-19 patients exhibiting severe disease (Dhama et al., 2020; Xu et al., 2020b). Lymphocytes such as natural killer (NK) cells, CD4 and CD8 are crucial for mounting antiviral immune response and their depletion in severe COVID-19 patients leads to immune collapse and enhanced mortality (Vardhana and Wolchok, 2020). Interleukin 7 (IL-7) plays an important role in the survival and expansion of lymphocytes (Laterre et al., 2020). Hence, administration of IL-7 offers a novel host targeted strategy in severe COVID-19 patients. A study conducted by Laterre et al wherein 12 COVID-19 patients received recombinant IL-7 on compassionate basis, reported that administration of IL-7 was well tolerated without exacerbated inflammation and restored the level of lymphocytes in critically ill COVID-19 patients. Another double blind randomised clinical trial involving 48 patients is going on in UK, to evaluate the effect of intramuscular administration of CYT107 (IL-7) on immune reconstitution in COVID-19 patients with reported lymphopenia, the results of the study are expected, soon (NCT04379076).

### 3.2. Glucocorticoids

**Dexamethasone:** Enhanced proinflammatory response is associated with the severity of COVID-19 disease; therefore, use of anti-inflammatory drugs at the right time might be helpful in the treatment of COVID-19 patients. In randomized multicentre clinical trial, dexamethasone, an anti-inflammatory synthetic glucocorticoid resulted in lowering of 28 day mortality in COVID-19 patients receiving oxygen support alone or mechanical ventilation, however, it did not offer any survival benefits in patients without oxygen support (Horby et al., 2021). Those who were receiving oxygen support, dexamethasone treatment was associated with lower risk of mechanical ventilation, whereas in patients already receiving mechanical ventilation, dexamethasone treatment improved the chances of successful cessation (Horby et al., 2021). Another meta-analysis of seven clinical trials using glucocorticoids including dexamethasone, methylprednisolone and hydrocortisone reported survival benefits in critically ill COVID-19 patients (Sterne et al., 2020).

### 3.3. Cytokine antagonists

**Tocilizumab:** Proinflammatory cytokines such as IL-6, TNF- $\alpha$  and IL-1 $\beta$  play a crucial role in progression of severe form of COVID-19. Tocilizumab, a recombinant monoclonal antibody against soluble and membrane bound IL-6 receptor was found to be beneficial in COVID-19 patients receiving tocilizumab in early studies from China (Xu et al., 2020a). Another observational study suggested mortality benefit in critically ill COVID-19 patients post tocilizumab treatment (Gupta et al., 2021). Further, a large randomized trial (n = 803) reported survival benefit of tocilizumab treatment in severely affected patients of COVID-19 (Gordon et al., 2021). Recently, US-FDA granted emergency use authorization (EUA) to tocilizumab for use in adults and children over 2 years of age with severe COVID-19.

**Anakinra:** Anakinra, a monoclonal antibody against IL-1 receptor has

the potential to block the effects of IL-1 $\beta$ , a proinflammatory cytokine associated with hyper-activated immune response in severely ill COVID-19 patients. A prospective cohort study in Paris, France, reported that anakinra treatment improved the clinical response in critically ill COVID-19 patients which reduced the need of mechanical ventilation and mortality without major side effects (Huet et al., 2020). A meta-analysis of four observational clinical studies (n = 184) reported that anakinra treatment was associated with reduced mortality and need for mechanical ventilation in COVID-19 patients with severe symptoms were reduced (Pasin et al., 2021).

### 3.4. Cell-based therapies

**Mesenchymal stem cells:** Mesenchymal stem cells (MSCs), have been used for the treatment of many inflammatory diseases such as graft versus-host disease (GVHD) and systemic lupus erythematosus (SLE) as cell-based therapy owing to its regenerative, differentiation and immunomodulatory properties; and found to be safe and effective in clinical trials (Hashmi et al., 2016; Leng et al., 2020). MSCs can directly interact with cells of immune system or secrete cytokines and modulate the immune response. Many clinical trials (NCT04615429, NCT03042143) are on going in various countries to investigate the efficacy of MSC treatment in COVID-19 patients and their efficacy data are awaited. In a recent study, Leng et al performed intravenous infusions of autologous MSCs in seven COVID-19 patients with pneumonia and observed that MSCs transplantation improved clinical outcomes of all the patients without any adverse effects. Most of the symptoms subsided within 2–4 days of MSCs transplant and pneumonia was significantly resolved as shown by the chest CT. All the patients turned RT-PCR negative within one to two weeks post MSC infusion. In critical patients, levels of inflammatory markers such as C-reactive protein (CRP) and TNF- $\alpha$  were decreased, and level of anti-inflammatory cytokine IL-10 was improved after MSC treatment compared to the control group. MSCs modulated the overall immune response and the population of cytokine-producing CXCR3<sup>+</sup>CD8<sup>+</sup> T cells, CXCR3<sup>+</sup>CD4<sup>+</sup> T cells and CXCR3<sup>+</sup> NK cells vanished in 3–6 days after treatment, whereas increase in the population of CD14<sup>+</sup>CD11c<sup>+</sup>CD11b<sup>mid</sup> regulatory DC cell population was observed (Leng et al., 2020). Thus, the data impart confidence to the host directed therapeutic potentials of MSCs for safe and effective treatment of COVID-19 patients with severe symptoms.

## 4. Development of novel HDTs against broad range of viral diseases including unknown viral pathogens

In the last couple of decades, the world has confronted an array of infectious outbreaks such as, SARS (2003), H1N1 (2009), MERS (2012), Ebola (2014), SARS-CoV-2 (2019). In order to intercept the forthcoming damages, there is an emergent need to improve our understanding on the mechanism of infectious diseases and host-pathogen interactions, which could subsequently be employed as tools and targets to prevent future epidemics. The ability to systematically assess and anticipate host factors contributing to the disease cycle would aid in better outbreak management. Hence, studies to identify group of viruses with potential to cause an epidemic need to be prioritised. Fundamentally, the known RNA virus family with air droplet mode of infection should be given importance because of their higher mutability and increased transmissibility. Viruses with track record of leaping from animals to humans should also be on the radar since all such viruses like smallpox, Ebola and HIV have been extremely devastating. Fortuitously, viruses from the same family share a lot in common; hence HDTs provide an excellent modality to stay vigilant even for the novel unknown viruses. By investigating the common host factors involved in each stage of a particular virus family, we can streamline the drug development process. A virus life cycle can be broadly classified into three stages: a. viral entry b. viral replication c. viral assembly and an in-depth detail of each stage would be useful for the development of novel HDTs. Further, modulating host cell immune

response could be applied against a wide spectrum of viruses and even for other infectious diseases. Some of the strategies and recent developments in this field are discussed below and summarized pictorially in Fig. 2.

#### 4.1. Viral host cell entry

Viral entry into host cell is aided by receptor interaction and is followed by penetration through or fusion with cellular membranes. Inhibitors targeting common host receptors, which are the front line of approach, should be the point of interest since they are largely shared in the same virus family. For example, both hepatitis B and hepatitis D virus use the same cell surface molecule, sodium taurocholate co-transporting polypeptide (NTCP) for host entry (Yan et al., 2012). Myrcludex-B (also called as bulevirtide) which blocks the NTCP receptor has been proclaimed as a safe and promising drug in its phase 2 clinical trial (Bogomolov et al., 2016). In a similar context, Maraviroc, a CCR5 receptor antagonist helps in cessation of HIV entry inside host T cells (Woollard and Kanmogne, 2015). In addition to cell surface receptors, viruses also depend on host proteases for their surface protein splicing which aid them in host entry (Böttcher-Friebertshäuser et al., 2013; Izaguirre, 2019). Aprotinin, a serine protease inhibitor which is in clinical use in Russia prevents influenza virus membrane fusion (Song et al., 2021a; Zhirmov et al., 2011). The effectiveness of aprotinin against SARS-CoV-2 has also been demonstrated at therapeutically achievable concentrations (Bojkova et al., 2020a). Targeting host factors, which directly affect viral entry, is a crucial parameter. There are several other commercial inhibitors that act at viral host cell entry and has been reviewed in detail in (Kumar et al., 2020).

#### 4.2. Viral replication

Host factors assisting in viral replication are major targets for HDTs. Host cell signaling through tyrosine kinases are known to play roles in viral replications along with their involvement in other stages (Kumar et al., 2011). Since targeting host factors involved in multiple stages of a viral life cycle, is of prime interest for a broader antiviral activity; research in receptor tyrosine kinase (RTK) inhibitors have gained massive attention. RTK inhibitors (like genistein and tyrophostin A9) have been found to be effective in multiple virus families (Dong et al., 2020; LeCher et al., 2019; Sauter et al., 2014). Many positive sense RNA viruses depend on host cell chaperone, cyclophilins (cypA) which aid in protein folding (Kovalev and Nagy, 2013). Besides facilitating protein folding, it is also involved in NF-AT mediated inflammation and protein trafficking. It is established that cyclosporine commonly used as an immunosuppressant forms a complex with cypA and can act as viral replication inhibitors (Nigro et al., 2013). Alisporivir and NIM-811 are some other molecules of the same category, which inhibit cypA with the advantage of being a non-immunosuppressant (Ma-Lauer et al., 2020). In addition to drug molecules, non-coding miRNAs that alter host gene expression and have been reported to influence viral infections, are another avenue to explore further as a mode of therapy. Appreciating the prospects of non-coding miRNA in therapy, several studies have identified miRNAs with pro-viral functions (Ho et al., 2011; Lanford et al., 2010; Rosenberger et al., 2017) while others have antiviral role (Gao et al., 2013; Lodge et al., 2017; McCaskill et al., 2017). Based on the function, miRNA antagonists or mimics approach could be applied, as appropriate. For instance, miRNA-122, which interacts with viral 5' UTR enhances hepatitis virus replication by stabilising the viral RNA and prevents them from RISC mediated killing (Shimakami et al., 2012). Miravirsin, a miRNA-122 antagonist is being investigated in phase 2

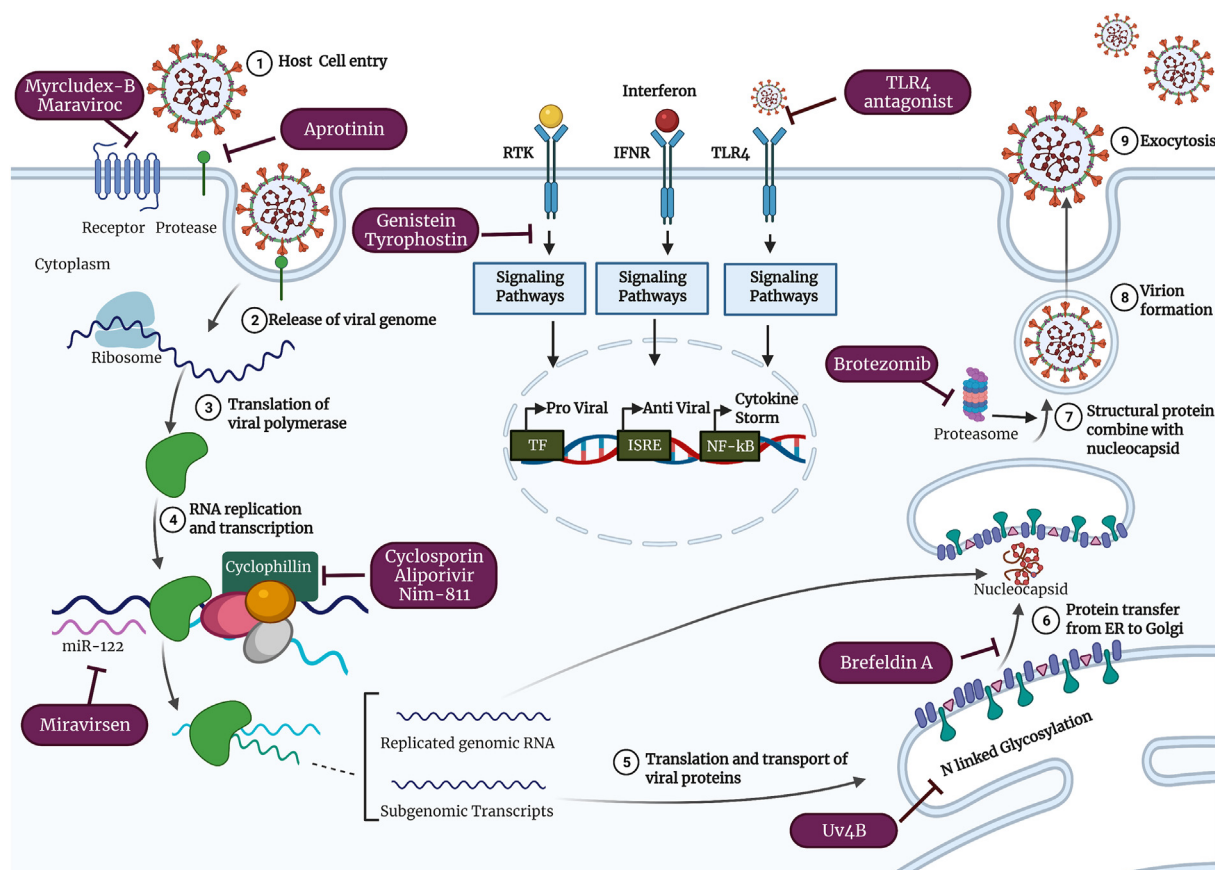


Fig. 2. Schematic of a Life cycle of an RNA virus (created with biorender.com) highlighting the mechanism of action of HDTs.

clinical trials (Janssen et al., 2013). On the other hand, miRNA34, the tumor suppressor miRNA in phase 1 clinical studies for multiple solid cancers, has shown to induce interferon responsive genes thereby suppressing dengue viral replication (Smith et al., 2017b; Wong et al., 2020). Despite the observed toxicity in cancer therapy, it would be interesting to see its effect in antiviral therapy.

#### 4.3. Viral assembly

It is the stage that involves the association of viral RNA into structural proteins called nucleocapsids in endoplasmic reticulum (ER), which are then transported to golgi bodies, where maturation and glycosylation occurs before they are secreted out. Several host proteins are involved in this process that play important role in trafficking and glycosylation. For instance, brefeldin A, which inhibits protein transport from ER to golgi disrupts the Dengue and Zika virus assembly (Raekiansyah et al., 2017). The iminosugar Uv4B, a potential inhibitor of alpha-glucosidases I and II interferes in glycosylation of Dengue and influenza proteins (Franco et al., 2021; Warfield et al., 2016a). There are also accumulating evidences of the proteasomal system involvement in regulation of virus assembly proteins (Choy et al., 2015; Haasbach et al., 2011). A clear mechanism has not been outlined but evidences of their involvement in several positive strand RNA viruses have been confirmed. Brotezomib, which works by targeting the proteasomal machinery, is in trial for curtailment of Zika virus (Dong and Kang, 2019; Widjaja et al., 2010).

#### 4.4. Immune response modulation

Immune modulation has been gaining massive popularity in the past few years for cancer therapy. It is now gradually being explored as a therapeutic option for a wide spectrum of viruses and other infectious diseases, too. They can be employed to enhance the protective immune defense or attenuate the aggressive response. Interferons produced by host cells render an antiviral immune response. On this rationale, numerous recombinants interferon or interferon inducers are in clinical use and has helped in fighting intracellular infections, particularly viral infections (Beglin et al., 2009). In contrast to enhancing protective immune response, HDTs can also be employed to suppress the exacerbated inflammation. The Cytokine storm, triggered by a multitude of cytokines, primarily by hyper-activation of TLR, is one of the collateral damage induced by immune system in its fight to clear infection. In this context, several TLR-4 antagonists such as eritoran, FP7 have been developed and have shown remarkable results in reducing collateral damages (Olejnik et al., 2018; Younan et al., 2017).

### 5. Strategies for identifying novel HDTs

#### 5.1. High throughput screening of pathway-based compound libraries

High throughput screening (HTS) is one of the most extensive approaches for identifying lead compounds with antiviral properties. By bringing together a combination of liquid handling devices, robotics, control software, and sensitive detectors into one method, HTS accelerates target analysis as multitude of compounds can be screened together at once. HTS is a multistep process which starts with the identification of a target, based on which assays are developed. These assays are initially validated with known positives and negative controls. A pilot study is initially carried out to assess the performance of the assay, which is followed by primary screening with a single fixed concentration of potential drug molecules. HTS becomes a convenient tool when already approved drugs are investigated for a new disease the application of approved drugs as new therapeutics is an emerging strategy since it accelerates drug development to a great extent.

Appreciating the advantage, this method offers in an emergency, several HTS screens were applied in response to the on-going pandemic against SARS-CoV2. Boceprevir, an FDA-approved HCV drug has shown

remarkable effectiveness with an EC50 of 1.90  $\mu$ M against SARS-CoV-2 virus infection (Ma et al., 2020). In another great effort, 12000 known drugs from LOPAC-1280 and ReFRAME library were screened for activity against SARS-CoV-2. The study identified 21 molecules with dose-activity relationships and 13 of them possessed antiviral activity at therapeutic achievable concentration (Riva et al., 2020). Likewise, in the past, HTS assays had yielded good leads such as emricasan (anti-helminthic), and niclosamide (caspase inhibitor) against Ebola and Zika virus. The group had screened for 6000 compounds that included approved drugs, clinical trial drug candidates and pharmacologically active compounds (Xu et al., 2016). Another important HIV drug Maraviroc, discussed earlier as viral entry inhibitor, is the outcome of an HTS program undertaken by Pfizer where the screen was against 500,000 compounds (Dorr et al., 2005). Hence, by applying already approved drugs in HTS, it takes a far better lead in response to the epidemic spreads. However, despite the swiftness, one major issue of HTS is the false negatives. The primary screen is mostly planned at a fixed concentration, and some potential molecules might get eliminated which can work at a higher concentration. It is important to note that all hit identification strategies have their pros and cons, and it is their apt application, which can fasten drug development.

#### 5.2. Genome wide screening methods to discover novel host factors for HDTs

Functional annotation of genetic elements and deciphering their association with diseases has been a demanding assignment. A systematic evaluation for the identification of host factors for various diseases has been lagging partly due to the lack of robust methods available for target identification. In this context, functional genetic screens have emerged as a powerful method for identifying potential targets of interest by establishing a direct relationship between the genotype and the phenotype. They furnish crucial information on gene function and their role in molecular events contributing to a phenotype shift. From times immemorial, scientists have been investigating molecular pathways without prior knowledge on the genes involved. This traditional forward genetic approach starts with a phenotype and trails down to genes contributing to the effect. This approach has been comfortably applied to a wide range of microorganisms and has immensely aided in deciphering complex life processes. However, the requirement of extensive morphological observations remains challenging in a more complex multi cellular organism. Newer approaches such as RNA interference (RNAi) and CRISPR/Cas screens have been gaining momentum to interrogate complex model systems in a high throughput manner. These methods are widely useful as pooled screens, where a large number of genes are being targeted in a population, which is then subjected to a selective pressure leading to enrichment or depletion of cells. The enriched cells are then subjected to NGS to reach the desired target accountable to the phenotype.

**RNAi:** In the early 2000, genome wide loss of function analysis using RNAi technology has unveiled a myriad of fundamental informations on gene functions (Clemens et al., 2000; Fraser et al., 2000), role of non-coding elements (Stojic et al., 2020) and their impact on disease associated pathways (Camargo et al., 2015). The basic working of RNAi is on the antisense approach wherein cellular RNA is being degraded thereby ablating gene expression. With the application of RNAi screen and subsequent network mapping among HCV, WNV (west Nile virus) and Dengue viruses (Flaviviridae family), some common pathways of TGF- $\beta$  signaling, ErbB signaling, MAPK signaling, and ubiquitin-mediated proteolysis were unveiled (Li et al., 2009). These pathways represent important shared host factors used by Flaviviridae. In another screen against Ebola virus, targeting 21,566 human genes, carbamoyl phosphate synthetase 2, aspartate transcarbamoylase, dihydroorotase (CAD), a tri-functional enzyme in the de-novo pyrimidine synthesis pathway emerged as one of the top hits from the screen which was subsequently confirmed with the effect of teriflunomide-a CAD inhibitor (Martin et al., 2018). The genome wide RNAi screen is a robust method for discovering genes

playing role in a pathway of interest. However, the major challenge of RNAi is to combat the off-target effects. Being an antisense approach, the off-target effects are high and since the execution is at post transcriptional level, the basal reduced expression is difficult to get rid of. Genome wide genetic screens are undoubtedly an accelerating platform for identification of novel host factors, but they also suffer from some caveats as evidenced by independent studies. For instance, the large scale screens carried for Influenza and HIV by independent groups yielded very limited redundancy in their target pathways (Chou et al., 2015). To overcome such problems, primarily, the essential host pathways should be identified first and then secondary screens with chemical inhibitors could propel the identification of the desired factor (Banerji et al., 2012; Gonsalves et al., 2011).

**CRISPR/Cas:** With the advent of the revolutionary CRISPR-Cas system, the above problems of RNAi were circumvented with minimal off-target effects (Smith et al., 2017a) and reduced basal expression. The off-target effects of CRISPR/Cas9 are significantly lesser compared to RNAi owing to the fact that it's a two-component system, where, in addition to the sgRNA base pairing with the endogenous RNA molecule, it requires the presence of a PAM sequence which is recognised by the Cas protein. Hence, there is a two-check system: the sgRNA base pairing and the PAM recognition, which imparts stringency to its cleavage. The second major limitation, i.e. incomplete loss of function is rescued to a large extent since the system works by blocking transcription initiation or extension depending on the region being targeted. Over all, the modularity and the ease that CRISPR-Cas offers are unmatched and hence is a widely preferred method in current times. CRISPR genetic screens can be carried out either by arrayed library or pooled library. In the arrayed library approach, each gene is targeted separately in a well and hence different phenotypic evaluation could be done. This approach is simpler but difficult to extend for a large-scale study. For a global study, pooled library is a better approach, where a library is primarily a number of lentiviruses created from a pool of unique DNA strands targeting different genomic regions. Pooled library is relatively cost effective and can be applied for a genome wide study. It is important to keep a good representation of sgRNA in the pooled library by having an optimum multiplicity of infection (MOI). It should not be too low that one misses out on the sgRNA representation in the library and it should not be too high that double integration events occur. A good screen depends largely on the sgRNA repertoire, and also on the stringency of phenotypic selection.

CRISPR genetic screens have imparted influential understanding of the host dependent factors in various viral parasites which include but are not limited to Zika, Dengue, and Influenza virus (Han et al., 2018; Li et al., 2019; Marceau et al., 2016). In an attempt to find the host factors influencing influenza virus replication, two independent rounds of screens were performed where the hits obtained from first screen were subjected to a secondary screen but with more sgRNA targets/gene. The strategy helped in gaining confidence in the hits by reducing false positives. Indeed, the group had found a significant number of hits overlapped with previous independent studies. In addition, they brought forward some novel host factors like WDR7, CCDC115 and TMEM199 influencing influenza virus life cycle (Li et al., 2020). Further, to identify the host factors important in SARS-CoV2, Wang et al. conducted lentivirus mediated genome wide CRISPR screen for mutations in host cells, rendering them resistant to the virus. They performed a similar screen with other coronaviridae family viruses (OC43 and 229E) and discovered two common host pathways-phosphatidyl inositol phosphate biosynthesis and cholesterol homeostasis as critical for infection (Wang et al., 2020). In a more recent work, novel host factors in SARS-CoV-2 infection using CRISPR screen were identified, which included the chromatin remodeling complex and the key components of TGF- $\beta$  signaling pathway (Wei et al., 2020). The identified pathways indeed assisted the SARS-CoV-2 replication, which was confirmed with low viral load in the presence of pathway inhibitors.

### 5.3. Proteomics based discovery of novel HDTs

Despite of having small genomes, viruses infect host cells by establishing complex protein-protein interactions (PPIs) with host cell signaling proteins. These virus-host-protein interactions strongly regulate the events of viral life cycle in the host and the virus-host interactome, that is created by the interplay between the viral PPI network (intraviral interactome) and the host PPI network (host interactome), is critical to the completion of viral lifecycle, evasion of host immunity and eventually the disease progression (Terracciano et al., 2021). Currently, the therapeutic modalities against the viral infections are limited and seems insufficient to combat the advent of any novel viral pandemic or drug resistance. In such scenario, mapping of the virus-host interactomes is instrumental in the identification of cellular protein networks crucial for viral life cycle. These host proteins which are perturbed by the viral proteins could be used as host directed antiviral targets for the novel drug development or repurposing of existing drugs (de Chassey et al., 2014).

To discover the direct interaction between viral protein and host protein, immune affinity purification coupled with mass spectroscopy (AP-MS), chemical cross linking, yeast two-hybrid systems and nucleic acid programmable protein array (NAPPA) screens are extensively used (Gillen and Nita-Lazar, 2019; Lum and Cristea, 2016). Among the experimental strategies to map PPIs, yeast-two hybrid screens are used to investigate direct binary interactions (Parrish et al., 2006) whereas genomic screens (Wei et al., 2021) and proteomics approaches like AP-MS and proximity-dependent biotin labeling (BioID) linked with MS offer more comprehensive PPI maps (Lum and Cristea, 2016).

AP-MS based techniques either with metabolic labelling, isobaric labelling or chemical cross linking, are used to identify accurate protein abundance, relative proteins levels, absolute protein quantification and identification of direct and weak transient interactions. Information obtained from AP-MS based proteomics, is important for the determination of PPI network, localization, signaling network and ligand protein interactions, which further contribute to drug target identification, drug design and drug repurposing (Gillen and Nita-Lazar, 2019; Jean Beltran et al., 2017; Lum and Cristea, 2016).

Proteomics based studies were performed for the evaluation of interaction of the viral pathogens such as HIV, Ebola, influenza, HCV, Zika with host cells to screen the potential host factor proteins for the drug design (Bösl et al., 2019; de Chassey et al., 2014; Li, 2015; Scaturro et al., 2019). Various studies and reviews based on proteomics approaches like time course proteomics, epigenetic proteomics, secretome analysis, cell signaling pathways-based proteomics and sub cellular proteomics have massively improved our understanding of infection mechanism, its interaction with target cells and immune system and offer a strong interaction map based on viral protein and host protein interaction for the identification of new drug targets and design of drugs (Bösl et al., 2019; de Chassey et al., 2014; Ma-Lauer et al., 2012; Viswanathan and Früh, 2007). In the recent and ongoing outbreak of SARS-CoV-2 also, various proteomics studies have identified potential viral-host interaction and host proteins as targets for the drug discovery or drug repurposing (Li et al., 2021; Sadegh et al., 2020; Schmidt et al., 2021).

In a recent study, Gordon et al cloned 26 proteins out of 29 proteins from SARS-CoV-2 genome, tagged and expressed in HEK-293T/17 to determine the physical interactions with host proteins using AP-MS that led to the identification of 332 high confidence PPI between viral and host proteins, involved in several biological processes such as replication, RNA processing and protein transport. This study identified 66 host proteins or factors as potential targets for the drug development or drug repurposing (Gordon et al., 2020). Another study using proteomic approaches reported that SARS-CoV-2 redesigned various metabolic pathways and translation machinery of the host for the establishment of infection and inhibitors targeting these pathways inhibited viral replication in cells (Bojkova et al., 2020b). Similarly, Stukalov et al reported that infection of SARS-CoV-2 in A549 cell line modified the proteome, phosphoproteome profile, ubiquitylation profile and down regulated TGF

beta and autophagy. They further screened the kinase inhibitors and matrix metalloproteinase inhibitors for their anti-viral potential on the basis of proteomic data obtained from SARS-Co-V2 infection in A549 cells (Stukalov et al., 2021).

Thus, proteomic studies with aim to discover PPIs in viral diseases, seem to have paramount importance in the development of novel HDTs.

## 6. Challenges

The COVID-19 pandemic has highlighted the drawbacks in public health infrastructure and its unpreparedness during a pandemic situation. Systemic investment in public healthcare system is the need of the hour to maintain the preparedness in event of any global viral outbreak in the future. Pre-emptive drug development against unknown viruses is vital to combat any future outbreak. Development of family specific or group specific antivirals is extremely important. However, due to higher mutability in viruses, DDAs become less effective, hence focus should be diverted on the development of HDTs. HDTs offer several benefits against viral infections however, development and deployment of HDTs in clinical settings is associated with certain challenges. Since host factors are crucial in various life processes of the host, targeting them may cause serious side effects. The major challenge with HDTs is a need for personalised therapy, which would demand an in-depth health profile screening of the individual. Further, despite offering an alternative to one drug – one drug, HDTs cannot be used as a full-fledged solo therapy and in majority of the cases, it can be used as adjunct to the current treatment regimen against the pathogen. Since most of the HDTs target the components of host immune system, the stage of the disease and timing of treatment becomes more important due to the dynamic nature of immune responses. The development of HDTs also suffers from the lack of a suitable model system as HDTs target human specific factors and readily available animal models do not truly represent the host.

## Funding

Department of Atomic Energy, India.

## CRedit authorship contribution statement

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

We acknowledge Department of Atomic Energy, India for its support.

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