

3	Posaconazole	antifungal	targets oxysterol-binding Protein and affects intracellular cholesterol distribution and disrupt cell membrane	DENV, ZIKV
4	Chloroquine Mefloquine,	Anti-malarial drugs	Inhibits stages of replication and inhibition of RNA synthesis.	DENV, ZIKV, CHIV
5	Minocycline	tetracycline antibiotics	binds to the bacterial 30'S ribosomal subunit and interferes with protein synthesis	West Nile virus, Japanese encephalitis virus
6	Sofosbuvir	antiviral	Inhibits RNA-dependent RNA polymerase	Zika virus
7	Emetine	Antiprotozoal	Inhibits NS5 polymerase	Zika virus
8	Niclosamide	Anthelmintic	Inhibit NS2B-NS3 protease	Zika virus
9	Nitazoxanide	Antiprotozoal	Inhibits the maturation of the viral hem agglutinin and the viral transcription factor.	Zika virus
10	Novobiocin	antibiotic	Protease inhibitor	Zika virus
11	Lopinavir/Ritonavir, Nelfinavir	Antiviral drug	Protease inhibitor	DENV
12	Suramin	Antiparasitic	Entry and fusion proteins inhibition	CHIKV
13	Suramin	Antiparasitic	Entry and fusion proteins inhibition	CHIKV
14	Amphotericin-B	antifungal drugs	Inhibit the replication	JEV
15	Chlorpromazine	Antidepressant	Inhibit viral entry <i>via</i> inhibition of clathrin-mediated endocytosis.	CHIKV, DENV, JEV, Zika
16	Imipramine	antidepressants	Entry inhibitor	CHIKV, DENV, JEV, Zika, WNV
17	Sertraline	antidepressants	Entry inhibitor	Zika virus
18	Suramin	Antiparasitic	Entry and fusion proteins inhibition	CHIKV
19	Suramin	Antiparasitic	Entry and fusion proteins inhibition	CHIKV

Drug repurposing for filoviridae

Filoviridae family of virus includes single stranded negative sense RNA viruses. Ebola virus and Marburg virus are the important members of this family. In the Democratic Republic of the Congo, close to the river Ebola, the first case of haemorrhagic fever was reported in 1976. 2014 to 2016; West Africa saw the largest and most serious outbreak Ebola endemic. Fruit eating bats from Pteropodidae family are the critical natural hosts for EBOV virus. The virus spreads to people either directly or indirectly through intermediate zoonotic hosts, contaminated areas, infected animals, infected people's organs, or direct contact with biological fluid discharges. Acute haemorrhagic fever is the primary symptom of EBOV's deadly disease, which has a very high mortality rate (90 percent).

Another virus of Filovirus genus is Marburg Virus (MARV). As like EBOLA it is filamentous, enveloped, no segmented, negative strand RNA virus [14]. There is still no therapeutic therapy for EBOV and MARV infections that has been approved and/or is being investigated. Rehydration with electrolytes is commonly considered one of the remedies for very extremely sick individuals. Because of its high mortality rate and the lack of an efficient and FDA approved treatment, Drug repurposing strategy will produce novel, effective therapeutic approach in a smaller duration of time which will be beneficial for critical endemic condition of EBOV. Preclinical DR investigations were carried out using live viruses as well as artificial viruses, and they resulted in the discovery of a number of certified medications that could offer protection against deadly EBOV infection in experimental animals. Drugs such as teicoplanin, imipramine, chlorpromazine, chlorcyclizine, sertraline, maprotiline, and diphenylpyraline, as well as benzotropine, promethazine, ketotifen, diphenhydramine, and others, may be repurposed for ebola treatment shown in Table 2.

Table 2. Approved and investigational repurposed drugs having potential against filoviridae (EBOV, Marburg).

1	Favipiravir	Influenza inhibition	Termination of RNA chain	EBOV
2	Teicoplanin	Antibiotic	Viral entry inhibitor	EBOV
3	Azithromycin	Macrolide antibiotic	Endocytosis inhibitor	EBOV
4	Brincidofovir	Human smallpox disease	-	EBOV
5	Chlorpromazine	tranquillizer	Endocytosis inhibitor	EBOV
6	Quinacrine	antimalarial	Viral entry inhibitor	EBOV

Drug repurposing for orthomyxoviridae

Influenza virus consisting influenza A (H1N1, H2N2, H5N1, H3N2, H7N9, etc.), influenza B, influenza C, influenza D belongs to Orthomyxoviridae family. These viruses are single stranded negative sense enveloped RNA viruses. Both influenza A and influenza B viruses caused severe pandemic situation in twentieth century all over world including H1N1 flu pandemic, H2N2 Asian flu epidemic, (H3N2 Hong Kong flu, H1N1 swine flu pandemic. Currently used drug which has mechanism of viral M2 ion channel inhibitor and neuraminidase inhibitors for treatment of influenza is now showing drug resistance. So repurposing is most promising technique for drug resistance influenza virus infection. Nitazoxanide, dapivirine, BAY 81-8781, clarithromycin, nalidixic acid and dorzolamide are most promising repurposed drug for influenza, whose details are given in Table 3.

Table 3. Approved and investigational repurposed drugs having potential against Orthomyxoviridae infection.

Drug repurposing for Orthomyxoviridae				
1	Clarithromycin/ Naproxen	Antibacterial	Inhibition of nucleoprotein which blocks virus transcription/replication.	Influenza
2	Nitazoxanide	Antiparasitic	Maturation of hem agglutinin	Influenza
3	Dapivirine	HIV	A non-nucleoside inhibitor of HIV-1 retro transcriptase	Influenza
4	Nalidixic Acid and Dorzolamide	antibiotic	Target mutant viral neuraminidase	oseltamivir-resistant influenza

Drug repurposing for retroviruses

Reverse Transcriptase (RT), an enzyme that transforms RNA genetic material into an intermediate form of DNA, is a characteristic of retroviruses. Retroviruses have drawn a lot of attention since they are linked to serious illnesses like cancer, AIDS, and neurological conditions [12-18]. At the end of 2020, there have been an approximately 37.7 million (30.2-45.1 million) HIV positive individuals worldwide, of which over two thirds (25.4 million) reside in the WHO African Region. With 36.3 million (27.2-47.8 million) deaths caused by HIV to date, it is still a significant global public health concern [19]. Reverse transcription, integration, and maturation are three crucial stages in HIV virus life cycle that are highly consistent among members of the retroviridae family. Antiretroviral drug discovery focuses on these 3 stages of virus life cycle. Zidovudine, the first anti-HIV drug to receive FDA approval, was first created as an anti-cancer drug in the late 1960's. Zidovudine was developed as an anti-HIV formulation following a large scale library screening strategy to hasten preclinical testing. Other repurposed drugs for HIV are shown in Table 4. A significant number of host components

have identified during the past two decades as possible cellular targets for anti-HIV treatments and, of special interest, for drug repurposing methods [20-29].

Table 4. Repurposed drugs for retroviruses (HIV).

1	Zidovudine	Anticancer	Reverse transcriptase inhibitor	HIV
2	Auranofin	Anti-rheumatic drug	Helps in promotion of differentiation and apoptosis of the memory CD4 ⁺ T-cell	HIV

Drug repurposing for Corona viruses

From starting of twenty first century, world is suffering from large scale epidemic and pandemics caused by highly infectious and deadly corona viruses. These Corona viruses are zoonotic viral infection which is enveloped and positive sense, single stranded RNA viruses. The crown shaped spikes on the surfaces of corona viruses give them their name. Corona viruses are divided into the alpha, beta, gamma, and delta subgroups [30-37]. In the middle of the 1960's, human coronaviruses were first discovered. The seven human infecting coronaviruses are

- 229E,
- NL63,
- OC43,
- HKU1,
- Middle East Respiratory Syndrome, or MERS.
- Severe Acute Respiratory Syndrome-1, or SARS.
- Severe Acute Respiratory Syndrome coronavirus 2 (SARS-cov-2).

Repurposed drugs for Covid 19 include polymerase inhibitors, protease inhibitors, malaria drugs, lipid lowering stains, rheumatoid arthritis drugs and some miscellaneous agents. In clinical trials, it was shown that remdesivir, a medication formerly used to treat viral illnesses like ebola and MERS-CoV, had some beneficial impacts against SARS-CoV-2. Chloroquine and hydroxychloroquine, two well-known antimalarial medications, have also been shown to be efficient against COVID-19 by reducing the viral load. List of repurposed drugs is shown in Tables 5 and 6.

Table 5. Direct acting antiviral drugs against Covid-19.

Sr.no	Drug	Mechanism of action	Original use	Repurposed for
Reverse transcription inhibitors				
1	Remdesivir	Targeting RNA-dependent RNA polymerase (Reverse transcription inhibitor)	Ebola virus infection treatment	Treatment of Covid-19
2	Favipiravir	Targeting RNA-dependent RNA polymerase	Influenza virus infection treatment	Treatment of Covid-19
3	Ribavirin	Targeting RNA-dependent RNA polymerase	Treatment of viral infections (HCV, RSV), and viral hemorrhagic fevers	Treatment of Covid-19
4	Tenofovir	Targeting RNA-dependent RNA polymerase	To treat HIV and HBV chronic infection	Treatment of Covid-19
5	Galidesivir	Targeting RNA-dependent RNA polymerase	Ebola virus disease and other viruses infections	Treatment of Covid-19
Protease inhibitors				
1	Lopinavir	Protease inhibitors	To treat HIV infection	Treatment of Covid-19
2	Raltegravir	Protease inhibitors	To treat HIV infection	Treatment of Covid-19
3	Niclosamide	Protease inhibitors	To treat worm infections. Also, SARS-Corona Virus, MERS-Corona Virus, ZIKV, JEV, HCV, EBOV, HRVs, CHIKV, and EBV.	Treatment of Covid-19

4	Darunavir	Protease inhibitors	To treat HIV infection	Treatment of Covid-19
5	Saquinavir	Protease inhibitors	To treat HIV infection	Treatment of Covid-19
Fusion inhibitors mimic to viral peptides and prevent the connections necessary for some enveloped viruses to fuse				
1	Camostat mesylate	Fusion inhibitor	For treatment of disseminated intravascular coagulation	Treatment of Covid-19
2	Umifenovir	Fusion inhibitor	For treatment and prophylaxis of influenza A and B infections, HCV, HBV, and ebola	Treatment of Covid-19
M2 ion channel protein blockers				
1	Amantadine	Inhibit M2 ion channel protein	Treatment of influenza infection	Treatment of Covid-19
2	Rimantadine	Inhibit M2 ion channel protein	Treatment of influenza infection	Treatment of Covid-19

Table 6. Approved and investigational host targeting antiviral with repurposed potential against Covid-19.

1	Chloroquine, HCQ	Inhibits cytokine production	Antimalarial	Treatment of Covid-19
2	Interferon β , interferon 2b	Increases immune response to viral infections by acting on target B cells through host interferon receptor and IFNAR1 signaling.		Treatment of Covid-19
3	Tocilizumab	Reduce cytokine response of host by binding and inhibiting IL-6 receptor	Rheumatoid arthritis	Treatment of Covid-19
4	Dexamethasone	Glucocorticosteroid with anti-inflammatory and immunosuppressant effect		Treatment of Covid-19
5	Statins	Lipid lowering drugs with anti-inflammatory and Immunomodulatory properties.		Treatment of Covid-19
6	Losartan and its derivatives/ARBS	Angiotensin receptor blockers	Antihypertensive	Treatment of Covid-19
7	Ruxolitinib, Baricitinib	JAK inhibitor	Inflammatory and autoimmune diseases including rheumatoid arthritis, psoriasis, and inflammatory bowel disease	Treatment of Covid-19

DISCUSSION

Challenges for antiviral drug discovery

- One drawback is that the antiviral effect seen *in vitro* is frequently not reproducible *in vivo*. eg- Lopinavir/Ritonavir, which suppressed Covid-19 in cultured cells but could not provide an advantage above standard therapy in patients when administered alone.
- Even though the efficient and promising outcomes in animal models cannot ensure efficacy in humans. Eg: The use of remdesivir to treat EBOV disease and Chloroquine to treat dengue fever.
- Broad spectrum antiviral is needed for drug repurposing as narrow spectrum antiviral drugs are not suitable.
- Drug safety in one disease condition may or may not guarantee the same safety in other disease conditions.
- Drug resistant for both direct acting and host targeting antiviral is the bottleneck for antiviral drug repurposing.

CONCLUSION

Although viral infections are acknowledged as a worldwide public health concern, most of them still lack effective vaccinations and effective antiviral medicines also the discovery of new specific antiviral needs a high cost and more time. Since now a day's strategy of discovering repurposed medications are an efficient way in case of discovering an urgent and cost-effective treatment for newly emerging viral infections as repurposed drugs have already undergone extensive testing (for toxicity, pharmacokinetics, pharmacodynamics, dosage, etc.) for their original indication. Repurposing them also reduces the clinical risks and requires comparatively less money and time. Drug repurposing has already shown very beneficial results with the pharmaceuticals that have been effectively repurposed, and this strategy can increase the opportunity to address the difficulties with resistance to antiviral and new viral threats. This article provides a summary of the effectiveness of numerous medications, categorized according to their mechanisms of action, against a variety of severe viral illnesses. Repurposed medications for a number of significant virus families, including the flaviviridae, filoviridae, orthomyxoviridae, retroviruses, and Corona viruses, are included in this review along with their prior usage and mechanisms of action. The medication repurposing strategy has produced candidates that show efficient effects in treating a variety of viral infections and can also be further investigated to get around the drug discovery barrier for newly emerging and re emerging viral contagious diseases.

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