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Review: Approved Heterocycles Based Antiviral Drugs

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ABSTRACT

Since the first principal antiviral drug, idoxuridine, was affirmed in 1963, 90 antiviral medications arranged into practical gatherings have been officially certified for the treatment of the accompanying nine human viral irresistible illnesses: (I) HIV infections (protein blocker, integrase viral enzyme inhibitors, passage inhibitors, glycosyl amines turn around transcriptase inhibitors, non-nucleoside control transcriptase inhibitors, and non-cyclic nucleoside phosphonate analogs), (ii) HBV Hepatitis B viral infection (lamivudine, interferons nucleoside inhibitor , furthermore, non-cyclic nucleoside phosphonate inhibitor), (iii) HCV Hepatitis C viral infection (ribavirin, interferon, NS3/4A protein blocker, NS5A inhibitors, and NS5B DNA polymerase activity inhibitors), (iv) Herpesvirus diseases (5-subbed 2 -deoxyuridine analogues, segment inhibitors, nucleoside analogs, pyrophosphate analogues, and non-cyclic guanosine analogs), (v) flu infection infections (ribavirin, grid 2 -protein blocker, RNA polymerase inhibitors, and neuraminidase inhibitors), (vi) Human cytomega- lovirus disease (non-cyclic guanosine analogs, non-cyclic nucleoside phosphonate analogs, pyrophosphate analogs, and oligonu-cleotides), (vii) Varicella-Zoster infection disease (non-cyclic guanosine analogs, nucleoside analogs, 5-subbed 2-deoxyuridine analogs, and antibodies), (viii) Respiratory Syncytial Infection (ribavirin and antibodies), and (ix) outside anogenital moles brought about by human papillomavirus disease (imiquimod, sinecat- echins, and podofilox). Here, we present just an outline of heterocycles antiviral medications endorsed in the course of the last 50 years a long time, revealing insight into the advancement of viable antiviral medicines against the current flow and developing irresistible infections around the world.

I. INTRODUCTION

Through the span of human progress, viral diseases have caused many humans to die around the world, driving the advancement of antiviral medications in a squeezing need. (1, 2). Another period of antiviral medication improvement has started since the main antiviral drug, idoxuridine, was endorsed in June 1963 (3). Since then, numerous antiviral drugs have been created for clinical use to treat a huge number of individuals worldwide. Between June 1963 and February 2020, nearly 90 drugs were officially affirmed to treat 9 human irresistible diseases (Table 1) regardless of how many antiviral inhibitors have been proposed in the literature. Previously, we inspected the historical backdrop of 25 endorsed antiretroviral drugs more than 25 years (1984 to 2009) and (June 1963 and April 2016), (4, 5,). The current examination common- speaks different heterocycles contain antiviral drugs affirmed for the treatment of 9 human infectious diseases in the course of recent decades. Approved heterocyclic antiviral drugs could be discretionarily separated in 13 functional groups (6).

Table 1.

Group*	Functional group chemical composition details.
i.	5-substituted 2-deoxyuridine analogs (n= 3) drugs and compounds);
ii.	Nucleoside analogs (n= 3);
iii.	Non-nucleoside pyrophosphate analogs (n=1);
iv.	Nucleoside switch transcriptase (RT) inhibitors (NRTIs) (n=9);
v.	Non-nucleoside invert transcriptase inhibitors (NNRTIs) (n=5);
vi.	Protease inhibitors (PIs) (n=19);
vii.	Integrase inhibitors (n=5);
viii.	Passage inhibitors (n=7);
ix.	Non-cyclic guanosine analogs (n=6);
x.	Non-cyclic nucleoside phosphonate (ANP) analogs(n=10);
xi.	Hepatitis C infection (HCV) NS5A and NS5B inhibitors (n=8);
xii.	Flu infection inhibitors (n=8);
xiii.	Immune stimulators, interferons, oligonucleotides, and antimitotic inhibitors (n= 8).

The inhibitory action of these approved drugs against 9 human infectious diseases and human viruses can be classified into DNA viruses (HBV, HCMV, HSV, HPV, and VZV), RNA viruses (HCV, RSV, and Influenza virus), and retroviruses (HIV), can be summarized in **Table 2**. Interestingly, some antiviral drugs have been approved to treat more than one infectious disease, suggesting that antiviral drugs may potentially treat multiple viral infections.

Table 2

Sr.No.	Human Viruses	Group Type* Drugs which may potentially treat for virus
1.	Human Immunodeficiency Virus (HIV)	iv, v, vi, vii, viii, and x
2.	Human Cytomegalovirus (HCMV)	iii, ix, x, and xiii
3.	Hepatitis B Virus (HBV)	ii, iv, x, and xiii
4.	Hepatitis C Virus (HCV)	vi, xi, xii, and xiii
5.	Herpes Simplex Virus (HSV)	i, ii, iii, viii, and ix

Sr.No.	Human Viruses	Group Type* Drugs which may potentially treat for virus
6.	Influenza Virus	xii
7.	Respiratory Syncytial Virus (RSV)	viii and xii
8.	Varicella Zoster Virus (VZV)	i , ii, viii, and ix
9.	Human Papilloma Virus (HPV)	xiii

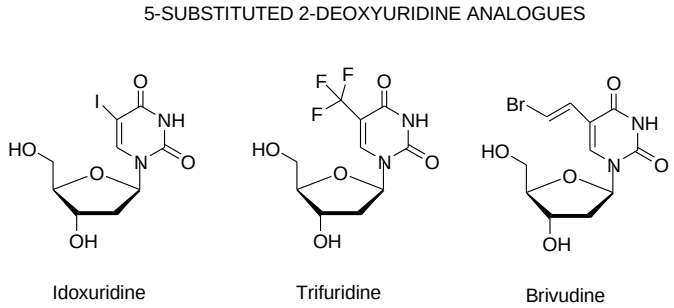
II. OVERVIEW OF HETEROCYCLES DRUGS USED TO DIAGNOSE NINE HUMAN VIRUSES INFECTIONS

The nine human infections depicted above have caused devastating infectious diseases that cause problems to huge number of people around the world. In that manner require the critical advancement of viable antiviral drugs. The accompanying areas centre on the molecular and therapeutic aspect of approved heterocycles antiviral drugs against these 9 human infections in 13 functional groups. Out of 13 functional groups here, 5 functional groups that based on antiviral drugs are summarized as below.

A) 5-SUBSTITUTED 2-DEOXYURIDINE ANALOGUES

Three antiviral drugs (idoxuridine, trifluridine, and brivudine [BVDU]) have been certified in the drug group of 5-sustituted 2-deoxyuridine analogs. Historically, the period of antiviral chemotherapies began in 1959 with the depiction of idoxuridine (5-iodo-2-deoxyuridine) by William H. Prusoff (7). While idoxuridine was initially described as a potential antitumor agent and later on became the first antiviral drug to be used (and it still is) clinically for the current treatment of herpetic eye infection (i.e., keratitis due to HSV). Herrmann was the first to count the antiviral activity of idoxuridine against HSV and vaccinia virus in1961 (8). After his, Heidelberger and Kaufman developing the effectiveness of trifluridine (5-trifluoromethyl-2-deoxythymidine) against HSV infections. (9). Idoxuridine and trifluridine are currently utilized for the topical treatment, (for example, in eye drops or eye ointment) against HSV epithelial keratitis (10). Idoxuridine and trifluridine alone can't be considered specific antiviral operators, they should be phosphorylated by cell kinases to the 5-triphosphate (TP) structure (i.e., idoxuridine) or the 5-monophosphate structure (i.e., trifluridine), and the two of which effectively hinder viral and cell DNA union (3). As a sample of the nucleoside thymidine, brivudine [(E)-5-(2-bromovinyl)-2-deoxyuridine] is exceptionally specific in its action against HSV-1 and VZV (11, 12). Besides, brivudine is better than idoxuridine, trifluridine, or acyclovir in cell culture tests (94). To accomplish its inhibitory action, brivudine is explicitly phosphorylated by the thymidine kinases of HSV-1 and VZV, which convert brivudine to its 5-mono-and 5-diphosphate structures. The cell nucleoside 5-diphosphate kinases promote phosphorylate of the 5-mono-and 5-diphosphates of brivudine into the 5-triphosphate of brivudine, which focuses on the viral DNA polymerase for the interference of viral DNA incorporation (11). BVDU has been endorsed in numerous nations everywhere throughout the world (aside from the United States and the United Kingdom) for the oral treatment of VZV disease, i.e., herpes zoster (shingles), for which it is recommended at a measurement of 125 mg for each day (for 7 days). Also, brivudine is utilized as eye drops for the treatment of HSV-1 epithelial keratitis, an orderly audit, which gathered information from 106 relative treatment preliminaries selecting 5,872 cases with HSV diseases, exhibited that treatment with brivudine at 14 days was at any rate as successful as a cyclo virus ganciclovir, two non-cyclic guanosine analogs (10). Ophthalmic arrangements of brivudine, trifluridine, acyclovir, and ganciclovir are similarly powerful, permitting 90% of treated eyes to recoup inside about fourteen days (10). Not at all like idoxuridine and trifluridine, which cause high harmfulness, brivudine

has a good security outline and can be controlled foundationally to treat HSV-1 and VZV (12). Also, brivudine may be utilized to treat Epstein-Barr infection (EBV) encephalitis (13, 14), but this new application presently can't seem to be demonstrated in clinical preliminaries. The chemical formula of idoxuridine, trifluridine, and brivudine as shown **Scheme 1**.

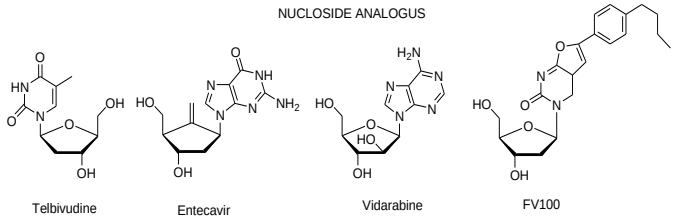


Scheme 1

B) NUCLEOSIDE ANALOGUES

The drugs gathering of nucleoside analogous incorporates three FDA-endorsed drugs: vidarabine, entecavir (ETV), and telbivudine (**Scheme 2**). Verifiably, arabinosyl nucleoside analogous was first segregated from wipes (15). Before Schabel (16) reported its antiviral potential, arabinosyl adenine was first viewed as a potential anticancer operator (17). With high strength against HSV and VZV (e.g. herpes zoster) infections, vidarabine, which targets viral DNA polymerases, was the first of the FDA-affirmed nucleoside analogous to be controlled foundationally in facilities (18, 19). In any case, vidarabine is scarcely solvent in watery medium, and it is quickly deaminated by adenosine deaminases to its inosine partner (ara-Hx [arabinosyl hypoxanthine]). Since June 2001, vidarabine has been ceased in the United States, presumably for business reasons (20). For the treatment of HBV infections, the following compounds have been authorized: (pegylated) interferons, lamivudine, entecavir, telbivudine, adefovir dipivoxil, and tenofovir disoproxil fumarate (TDF). Lamivudine and TDF have likewise been authorized for the treatment of HIV diseases and are additionally talked about beneath. Two nucleosides analogous, entecavir and telbivudine are only utilized for the treatment of HBV diseases. In patients with either HBeAg-positive (HBeAg) constant hepatitis B (21) or HBeAg-negative incessant hepatitis B (22), the paces of histological, virological, and biochemical enhancements were significantly higher with entecavir than with lamivudine. All the more critically, long haul observing of nucleoside-guileless patients accepting 5 years of entecavir treatment demonstrated a low pace of HBV protection from entecavir (23). Notwithstanding, it came as an unexpected when entecavir was accounted for to restrain HIV-1 diseases with just humble action (24, 25), on the grounds that this may create HIV-1 protection from entecavir in patients co-tainted with HIV-1 and HBV. The "bring home" message was not to utilize entecavir in such patients (25). A few stages 2 or 3 clinical preliminaries thought about the potencies and securities of telbivudine versus lamivudine, and their findings proposed that telbivudine offered more prominent HBV DNA concealment with less obstruction than lamivudine (26-28). For example, a randomized, twofold visually impaired, stage 3 preliminary enlisted 1,367 patients infected with ceaseless HBV recommended that telbivudine was better than lamivudine as far as higher paces of imperceptible viremia and less opposition (29). For treatment of HBeAg moms during late pregnancy, telbivudine was very much endured, with no extreme reactions in telbivudine-treated moms or their babies (30). In spite of the fact that entecavir is better than telbivudine in well-being, both telbivudine and entecavir offer comparative medication efficacies as far as the combined paces of imperceptible HBV DNA and alanine aminotransferase levels (31). For first-line treatment of HBV diseases, the utilization of entecavir is forcefully suggested, particularly in youngsters matured 2 to 12 years (32). Nevertheless, telbivudine, lamivudine, and adefovir dipivoxil are not prescribed because they have a low obstruction to opposition. Generally speaking, orally directed nucleoside

analogous, with their security, simple use, and low drugs opposition rates, are best for HBV treatment, yet the significant expenses of these drugs stay an incredible worry in asset constrained regions. In this way, lamivudine is normally utilized in first-line treatment paying little heed to its high pace of medication obstruction (33).

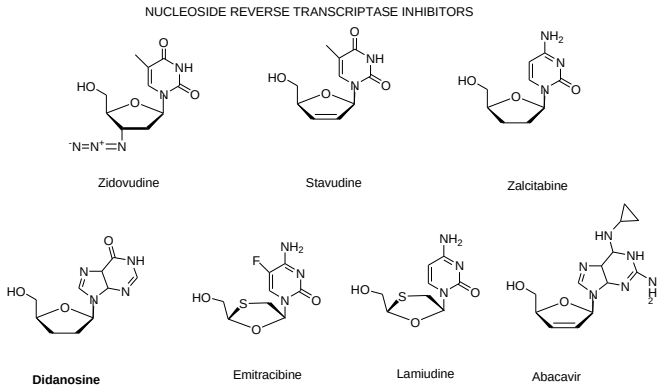


Scheme 2

C) NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

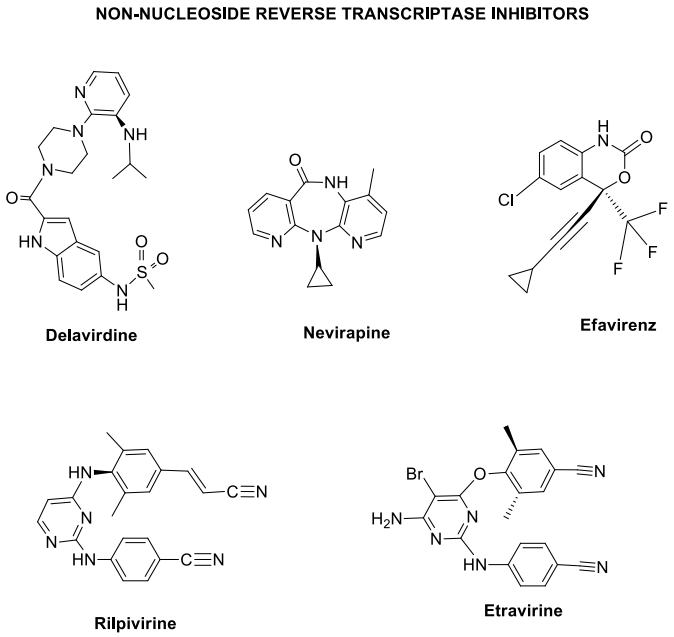
Not long after its revelation as an enemy of HIV consultant in 1985 (34), Zidovudine (AZT [azido-thymidine] was certified for clinical use in 1987. Zidovudine can't be the first tranquilize affirmed for HIV treatment yet in addition the first medicate in the gathering of NRTIs, which target HIV invert transcriptase to meddle with viral converse translation (**Scheme 3**). Stimulated by the achievement of zidovudine, 6 medications in the gathering of NRTIs were along these lines endorsed to treat HIV or HBV diseases: (I) didanosine (ddI [2,3-dideoxyinosine]) (35), (ii) zalcitabine (ddC [2,3-dideoxycytidine]) (35), (iii) stavudine (d4T [2,3-didehydro-3-deoxythymidine]) (36-38), (iv) lamivudine (3TC [2,3-dideoxy-3-thiacytidine]) (39), (v) abacavir (ABC) [(1S,4R)- 4-(2-amino-6-(cyclopropyl amino)- 9H-purin-9-yl)- 2-cyclopentene-1-methanol] (40), and (vi) emtricitabine [FTC (2,3-dideoxy-5-fluoro-3-thiacytidine), where demonstrates the L-enantiomeric form] (41). All NRTI compounds are known as 2, 3-dideoxynucleoside analogs, with comparable systems of medication activity. After their phosphorylation to the 5-TP, NRTIs go about as chain eliminators, a component of drug activity at first appeared for AZT (42), with (i) AZT-TP in rivalry with dTTP (43), (ii) ddATP (shaped from ddI) in rivalry with dATP, (iii) ddCTP (framed from ddC) in rivalry with dCTP, (iv) d4T-TP (framed from d4T) in rivalry with dTTP, (v) 3TC-TP (shaped from 3TC) in rivalry with dCTP, (vi) carbovir-TP (shaped from ABC) in rivalry with dGTP, and (vii) FTC-TP [formed from FTC] in rivalry with dCTP (4) . NRTIs alone are not controlled in HIV medications since NRTIs for the most part have a low hereditary boundary to the improvement of medication obstruction transformations, which have been portrayed by the International Antiviral Society-USA (IAS-USA) board (44) and the HIV tranquilize opposition database (http://hivdb.stanford.edu/). NRTIs are generally controlled with different medications in exceptionally dynamic enemy of retroviral treatment (HAART) to focus on numerous phases of the HIV life cycle (45, 46). Specifically, both lamivudine and emtricitabine are spines in 9 endorsed blend drugs (I) lamivudine in addition to zidovudine (Combivir); (ii) lamivudine in addition to zidovudine and ABC (Trizivir); (iii) lamivudine in addition to the integrase inhibitor dolutegravir (Dutrebis); (iv) lamivudine in addition to dolutegravir and abacavir (Triumeq); (iii) emtricitabine in addition to TDF (Truvada); (iv) emtricitabine in addition to TDF and efavirenz (Atripla); (v) emtricitabine in addition to TDF and the NNRTI rilpivirine (Compleraor Eviplera);(vi) emtricitabine in addition to TDF, the integrase inhibitor elvitegravir, and cobicistat (Stribild);(vii)emtricitabine in addition to tenofovir alafenamide (TAF), elvitegravir, and cobicistat (Genvoya); (viii) emtricitabine in addition to TAF and rilpivirine (Odefsey); and (ix) emtricitabine in addition to TAF (Discovery). In spite of the fact that the pharmacological identicalness and clinical compatibility of lamivudine and emtricitabine remain discussed (47, 48), the two medications are key parts of endorsed blend drugs. In clinical practice, the most widely recognized reactions with NRTIs are reversible fringe neuropathy, nausea, headache, rash, anemia, leukopenia, pancreatitis, gout, or hyper sensitivity (49). It is additionally worth referencing that as a result of its neurotoxicity, the FDA endorsed operator

zalcitabine has been ceased since December 2006. Starting today, NRTI drugs, licensed for the most part before 2003, are over their termination dates for licenses (50). Patent lapse in this way invigorates expansive promoting around the world, making NRTIs main stream first-line operators against HIV diseases in asset constrained zones.



Scheme 3

while utilized because of its high risk, generally low intensity, and complex medication collaborations (61).



Scheme 4

D) NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Found in the late 1980s, the gathering of NNRTIs incorporate five affirmed antiviral HIV drugs: nevirapine, delavirdine, efavirenz, etravirine, and rilpivirine (**Scheme 4**). Generally, NNRTIs began from two classes of compounds found autonomously from one another: 1-[(2-hydroxy-ethoxy) methyl]-6-phenylthiothymine (HEPT) analogs (51, 52) and tetrahydro-imidazo [1, 4]-benzodiazepine-2(1H) - one and - thione (TIBO) analogs (53). To control viral replication, HEPT and TIBO substituted target HIV-1 opposite transcriptase (54–56). Emivirine (MKC-442), got from the HEPT substituted (57), had arrived at stage 3 clinical preliminaries before its further advancement was halted (58). TIBO substituted group through an exceptionally meandrous course to the identification of diaryl pyrimidines (DAPY) derivatives (59), including dapivirine, etravirine, and rilpivirine (60). Affirmed by the FDA, etravirine and rilpivirine joined by three different NNRTIs (delavirdine, efavirenz, and nevirapine), and are currently available. Delavirdine is presently once in a

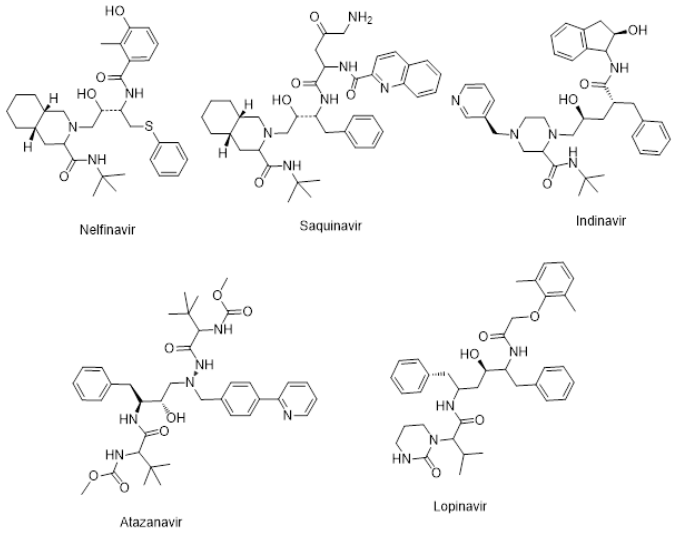
E) PROTEASE INHIBITORS

In the class of protease inhibitors (PIs), 12 HIV protease molecules and 7 HCV NS3/4A protease molecules were affirmed for clinical use. HIV and HCV protease inhibitors have discussed under below.

HIV PROTEASE INHIBITOR

Generally, HIV-1 protease was first proposed as a potential objective for AIDS treatment by Kramer and co-workers. (62), when they indicated that a casing shift change in the protease area of the polygene blocked protease- binding cleavage of suffer precursor proteins (63). The change state mimetic idea later extended by Roberts et al to show the reasonable structure of peptide-based protease inhibitors (63). In 1995, saquinavir was endorsed as the first protease inhibitor, denoting the start of a period for this new class of hostile to HIV inhibitors. Truth be told, saquinavir as well as 9 out of the 10 endorsed HIV protease inhibitors depend on a similar standard, wherein the hydroxyethylene security goes about as the peptidomimetic platform, including saquinavir, indinavir, nelfinavir, lopinavir, atazanavir, **(Scheme 5).** The only exemption is tipranavir, which is built on the coumar in scaffold (64). When protease inhibitors

rival common substrates of HIV protease as the peptide mimetic framework (65), amino acid varieties close to this platform and inside the cleavage general of protease substrate (i.e., Gag and Gag-Pol gens) may have been chosen during infection advancement to make obstruction HIV protease drugs (66). With the exception of the ceased active operator amprenavir (Agenerase), which is supplanted by fosamprenavir, other protease inhibitors are still broadly utilized for HIV diseases. Normal reactions with PIs are nephrolithiasis, hypertension, rash, and diarrhea, elevation of liver enzyme levels, ingrown toenails, amiable hyper bilirubinemia, and gastrointestinal miracle.



Scheme 5

F) Heterocyclic drugs in COVID-19 pandemic

The COVID-19 pandemic progresses unabated in many regions of the world. An effective antiviral against SARS-CoV-2 that could be administered orally for use following high-risk exposure would be of substantial benefit in controlling the COVID-19 pandemic. Herein, we show that ***Molnupiravir*** (MK-4482), an orally administered nucleoside analog, inhibits SARS-CoV-2 replication in the Syrian hamster model. The inhibitory effect of MK-4482 on SARS-CoV-2 replication is observed in animals when the drug is administered either beginning 12 h before or 12 h following infection in a high-risk exposure model. These data support the potential utility of MK-4482 to control SARS-CoV-2 infection in humans following high-risk exposure as well as for treatment of COVID-19 patients (67).

Remdesivir is an intravenous nucleotide prodrug of an adenosine analog. Remdesivir fixes the viral RNA-dependent RNA polymerase and inhibits viral replication through premature termination of RNA transcription. It has verified in vitro activity against SARS-CoV-2. (68). In a rhesus macaque model of SARS-CoV-2 infection, remdesivir treatment was initiated soon after inoculation; the remdesivir-treated animals had lower virus levels in the lungs and less lung damage than the control animals. (69). Remdesivir is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg). It is also available through an FDA Emergency Use Authorization (EUA) for the treatment of COVID-19 in hospitalized pediatric patients.

On May 8, 2021, the Drugs Controller General of India approved 2-Deoxy-D-glucose an anti-COVID oral drug, developed by DRDO India, for emergency use as an adjunct therapy in moderate to severe coronavirus patients based on this compound. The drug comes in powder form in a sachet, which is taken orally by dissolving it in water. Clinical trial results have shown that 2-DG helps in faster recovery of hospitalized patients and reduces supplemental oxygen dependence. (70).

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