

Tenofovir as a Treatment for COVID-19

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Abstract

After the emergence of SARS-CoV-2 - the cause of COVID-19 - we need an effective antiviral agent to stop the spread of this epidemic. Tenofovir (of the same pharmacological group as Remdesivir) speeds up recovery in COVID-19 patients by inhibiting viral RNA polyphens. Tenofovir could be an option for treating COVID-19 patients due to its good availability in the pharmaceutical market and many studies on its therapeutic properties and effects over a long period of time (such as treatment of HIV and hepatitis B virus) and its acceptable price in many countries (especially Third World countries) compared to other proposed drugs for treating Covid 19.

Keywords: *Tenofovir; COVID-19*

Background

In December 2019, thousands of pneumonia of unknown origin cases were reported in Wuhan, China, which were later determined to be caused by a virus called novel coronavirus, then called later severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease is caused by this new fatal virus named coronavirus disease 2019 (COVID-19) [1]. By this time, millions of cases and deaths are reported to be caused by this virus [2]. The SARS-CoV-2 possesses enveloped club-like spike protein projections with positive-sense large RNA genome and has a unique replication strategy, such as Middle East respiratory syndrome (MERS), hepatitis C virus (HCV), HIV virus, Ebola virus, rhinoviruses and others. These viruses have a similar replication mechanism requiring an RNA-dependent RNA polymerase (RdRp) [3]. Older patients (> 70 years) and those with comorbidities (cardiovascular disease, diabetes mellitus, etc.) have the most severe disease. Severe complications and death are more common in immunely-compromised patients [4]. Despite that so far there is no specific treatment for COVID-19, many potential treatments ae being evaluated [5]. To date, several potential drug candidates, including lopinavir/ritonavir (Kaletra), nucleoside analogues, neuraminidase inhibitors, remdesivir, DNA synthesis inhibitors (such as tenofovir disoproxil and lamivudine), and chloroquine, have been proposed [6]. Coronavirus replication is the target of any development drug under investigation. In particular, coronavirus RdRp is the main target of the drugs. Whether any of these drugs could prevent harm or death to treated coronavirus patients or not is a question the WHO is addressing through its global trial SOLIDARITY [7]. We try giving tenofovir for coronavirus disease 2019 (COVID-19) patients, which is cheap and available in the pharmaceutical market worldwide. Coronaviruses are a type of enveloped positive-sense RNA synthesis of DNA (Figure 1) could inhibit COVID-19 virus multiplication. Viruses with an extra-large RNA genome and are characterized by projections resembling a club on the surface. Coronaviruses have a unique replication mechanism through which antiviral drugs could be potentially effective in SARS-CoV-2 cases such as nucleoside analogues (a polymerase inhibitor). Tenofovir disoproxil, lamivudine and other nucleoside analogues that inhibit [8]. this polymerase shares similar catalytic mechanisms and displays active site conservation among different positive sense RNA viruses, including coronaviruses and HCV [9]. Nucleotide analogues that inhibit polymerases are an important group of antiviral agents [10]. HCoVs are long, single-stranded RNA viruses with positive sense

RNA. HCoVs are characterized by two groups of proteins: structural proteins and non-structural proteins. Spike (S) present in all coronaviruses, nucleocapsid (N), matrix (M) and envelope (E) are the structural proteins while proteases (nsp3 and nsp5) and RdRp (nsp12) are examples of non-structural proteins [11]. RdRp is an essential viral enzyme in the life cycle of RNA viruses [12].

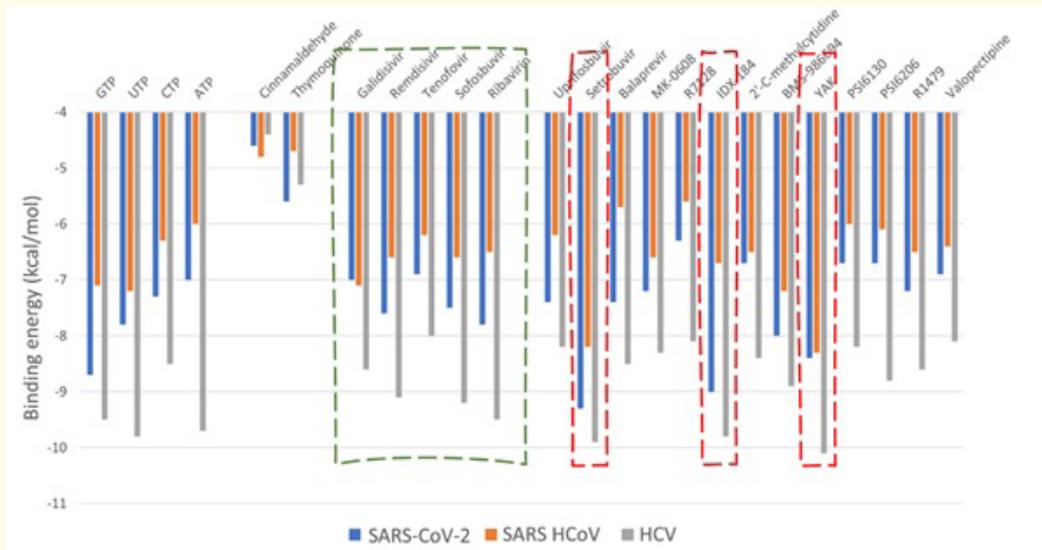


Figure 1: The dashed green box marks the five drugs (approved by the FDA against HCV, EBOV, and HIV). In this figure, we can see that tenofovir has proven effective and binding capacity of up to 6.8 in binding the protein against the Covid 19 virus [12].

Tenofovir disoproxil fumarate (tenofovir DF)

Tenofovir disoproxil fumarate (tenofovir DF) is a precursor of tenofovir, a nucleotide (nucleoside monophosphate) analogue effective against retroviruses, such as HIV-1 and HBV. Tenofovir is administered orally and exhibits longer half-lives both in serum (17 hours) and intracellularly (≥ 60 hours) than other nucleoside analogues, thus supporting a flexible dosage schedule (once daily). Tenofovir DF caused no clinically significant drug interactions. Tenofovir is administered orally in adults in 300 mg dosage a day and is eliminated renally, via tubular secretion; thus dose-interval adjustments for tenofovir DF should be made in patients with renal impairment. No adjustment in dosage of tenofovir DF is needed in patients with liver disease [13]. Oral tenofovir DF in dosage of 300 mg once daily proved effective in reducing viral load in patients with HIV infection [14]. The activation process undergoes through a series of hydrolases reactions to the deprotected monophosphate form and then sequentially phosphorylated by two kinase reactions to create the triphosphate form tenofovir diphosphate (TFV-DP).

TFV-DP is the active form and is an acyclic nucleotide with no 3'-OH group (which is a molecule associated by both HIV and HBV polymerases). The absence of this group stops nucleic acid elongation and thus prevents viral replication. TDF, a precursor of tenofovir, acts as a nucleoside analogue reverse transcriptase inhibitor [15]. Tenofovir disoproxil and remdesivir, two medications of the same class, are believed to speed up the recovery of COVID-19 via inhibiting synthesis of viral RNA polymerase. No comprehensive data are available about the mechanism of action behind use of tenofovir in COVID 19 patients. Nevertheless, efforts are put to further comprehend the efficacy and safety of the drug [16].

Review of clinical trial

TFV-DP is approved by the FDA for the treatment of HIV and hepatitis B virus (HBV) infection. A study tested the efficacy of the active triphosphate form of tenofovir alafenamide as a SARS-CoV-2 RdRp inhibitor [3]. Giuliano C. Clososki and his colleagues concluded in their

study that the biological assay indicated that TDF is promising in treating COVID 19 in vitro, and we hope that there will be more clinical trials to prove that [14]. Elfiky, *et al.* compared the binding energy to SARS-COV 2 RdRp between possible COVID-19 drugs, including tenofovir and Remdesivir; and as you see in the paragraph below, remdesivir and tenofovir have too close binding energy and efficacy against SARS-COV2 RdRp and predict that ribavirin, remdesivir, sofosbuvir, galidesivir, and tenofovir may have inhibitory activity against SARS-CoV-2 RdRp (Figure 1) [12]. Minchen Chien., *et al.* studied the replication process of hepatitis C virus and coronavirus replication and analyzed the molecular structures and activities of viral inhibitors. They proposed Sofosbuvir triphosphate as a possible inhibitor of SARS-CoV-2 RdRp [3]. In a systematic review by Nathan Ford and his colleagues, results were inconclusive on whether antiretrovirals could prevent infection among patients at high risk of acquiring COVID-19 or even improve outcome [17]. Härter., *et al.* studied 6 patients infected with HIV and COVID 19 who were on tenofovir and other antiretroviral drugs. The six patients were discharged from the hospital after all; five of them had mild pneumonia, and one patient had severe disease and was admitted to the intensive care unit before improvement and discharge [18]. This study does not prove that tenofovir has an independent role in treating SARS-COV 2 but gives us a sign that this affordable drug can be a low economic country hope. In a study of coinfection of COVID 19 and HIV performed in the USA that included 93 patients, 69.6% of them were on tenofovir and showed no significant differences between the tenofovir group and the other group treated with other drugs. However, some researchers suggested that HIV patients on antiretroviral therapy (ART) could have lower risk for COVID-19 as such medications may be effective against coronaviruses such as SARS-CoV-2 [19]. Others suggested the use of Tenofovir alafenamide, another tenofovir prodrug safer than tenofovir disoproxil in patients with renal impairment. The two drugs are under clinical trials testing the activity of Tenofovir alafenamide as a possible treatment and tenofovir disoproxil as a possible prophylactic drug [20]. As SARS-Cov-2 mutates over time, the recommended drugs change accordingly, therefore studying the mutations is an important part in predicting possible drugs. We noticed that six drugs are being mainly recommended, Remdesivir, Sofosbuvir, Ribavirin, Taribavirin, Tenofovir alafenamide and Vidarabine [21]. Tenofovir disoproxil, abacavir, lamivudine and other antiviral drugs which inhibit RNA synthesis as nucleoside or nucleotide analogue inhibitors might have activity against SARS-CoV-2. This possibility is driving clinical trials to test tenofovir disoproxil use as a prophylactic treatment against COVID-19 in healthcare worker [21]. SARS, MERS and SARS-CoV-2 coronaviruses, such as HCV and flaviviridae are single stranded RNA viruses that share a positive sense structure and a similar replication mechanism requiring. These viruses replicate via an important enzyme, RNA-dependent RNA polymerase (RdRp). It is possible that RdRp can be targeted by HCV/HIV nucleoside/nucleotide analogues as a binding site thus potentially inhibiting virus replication. Further research is needed to explore tenofovir as a candidate to treat SARS-COV-2 [5].

Conclusion

With the emergence of SARS-CoV-2, the causative agent of COVID-19, we need an effective antiviral agent to stop the current outbreak. It can be suggested that tenofovir may be an option for treating COVID-19 patients, especially because of its good availability in the pharmaceutical market and its therapeutic properties and side effects over a long period of time (as a treatment for office HIV and hepatitis B virus, as well as its acceptable price in many countries (especially Third World countries) compared to other proposed drugs for treating Covid 19.

Competing Interests

None of the authors have any competing interests.

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