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Efficacy of tenofovir on clinical outcomes of COVID-19 patients: a systematic review

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Abstract

Background Pharmacological treatments for COVID-19 remain limited, particularly for severe outcomes. Tenofovir, an inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), has been proposed as a therapeutic agent to reduce hospitalization, intensive care unit (ICU) admissions, and mortality.

Objective To assess the efficacy of tenofovir in COVID-19 patients based on randomized controlled trials (RCTs).

Methods A systematic review of RCTs assessing tenofovir in COVID-19 was conducted. Searches in PubMed/MEDLINE, Scopus, Cochrane Library, LILACS, SciELO, and COVID-19 LOVE databases were last updated on April 16, 2025. Risk of bias was evaluated using the Cochrane Risk of Bias 2.0 tool. As a meta-analysis was not feasible, a qualitative analysis was performed. The review protocol was registered in PROSPERO (CRD42023465336).

Results Among 1241 retrieved trials, three met the inclusion criteria. These trials, conducted in 32 hospitals across Colombia, Spain and Iran included 1048 patients. In the Colombian study, the combination of tenofovir disoproxil/emtricitabine with colchicine and rosuvastatin was associated with reduced 28-day mortality (risk difference [RD] = -0.05; 95% CI: -0.07 to -0.04) and lower need for invasive mechanical ventilation (RD = -0.08; 95% CI: -0.11 to -0.04). However, randomization bias and small sample size limit the interpretation of these results. Conversely, the Spanish study was classified as having a low risk of bias, but found no significant benefit of tenofovir disoproxil/emtricitabine in reducing 28-day mortality (risk ratio [RR] = 1.76; 95% CI: 0.52 to 5.91) or for the composite outcome of ICU admission, disease progression, and mortality (RR = 0.95; 95% CI: 0.66 to 1.40). The Iranian study, in turn, demonstrated that tenofovir alafenamide, when combined with standard treatment, significantly reduced the need for mechanical ventilation (0.0% vs. 13.3%, $p = 0.038$) and ICU length of stay (3.3 days vs. 14.5 days; $p = 0.04$). However, the presence of a high risk of bias, with major concerns regarding co-interventions and statistical analyses, precludes a definitive conclusion regarding these results.

Conclusions This review identified three clinical trials evaluating the efficacy of tenofovir in COVID-19, with conflicting results. One study suggested a potential benefit in reducing mortality and the need for invasive mechanical ventilation in mild to moderate cases but methodological limitations, including risk of bias and small sample size, weaken its conclusions. The second study found no significant impact on mortality or disease progression. In the third study, no deaths were reported, but he significant reduction in the need for mechanical

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ventilation and ICU length of stay is extremely limited due to the high risk of bias. Given these inconsistencies and the limitations of available evidence, tenofovir cannot be recommended for COVID-19 treatment.

Keywords COVID-19, Tenofovir, Treatment outcome, Mortality, Systematic review

Background

Worldwide, 777,3 million cases of COVID-19 have been recorded, with more than 7 million deaths by early February 2025 [1]. Despite significant advances in vaccination and supportive care, effective pharmacological treatments for COVID-19 remain limited, particularly for severe cases [2, 3]. Current therapeutic strategies rely primarily on antivirals, corticosteroids, immunosuppressants, and anticoagulants, but their effectiveness varies, and new therapeutic options are still needed [4–6].

Among the available antivirals, molnupiravir, nirmatrelvir-ritonavir, and remdesivir have been recommended for the treatment of COVID-19 [7]. While remdesivir is recommended for hospitalized patients without oxygen requirements but at risk of progression, severe cases may require dexamethasone, immunosuppressants, and anticoagulation — primarily with low-molecular-weight heparin due to the high risk of thromboembolic complications [8, 9]. However, these treatments have limitations, reinforcing the need to explore additional therapeutic alternatives, especially for patients with severe disease [10, 11].

In this aspect, drug repositioning has emerged as a promising strategy for identifying effective treatments for COVID-19. By repurposing existing medications, this approach reduces development costs, shortens regulatory timelines, and accelerates clinical implementation [12–14]. Over the years, drug repurposing has successfully expanded treatment options for various conditions [15–20], and it has been extensively explored in the context of COVID-19 [21–23]. While some repurposed drugs, such as chloroquine, hydroxychloroquine, ivermectin, and nitazoxanide, failed to demonstrate clinical efficacy in meta-analyses of randomized trials [24–27], numerous other drugs remain under investigation [22, 23, 28–30]. Among these candidates, antiretrovirals demonstrate high potential for inhibiting the replication process, in addition to accelerating the natural clearance of SARS-CoV-2 [31–36].

Among the antiretrovirals, tenofovir was identified as an inhibitor of the RdRp (RNA-dependent RNA polymerase) of SARS-CoV-2 [32, 33]. Observational studies suggest that tenofovir may reduce hospitalization rates, intensive care unit admissions and mortality from COVID-19 [37–39]. However, conflicting evidence exists, with some studies indicating that tenofovir does not significantly impact viral replication or disease progression [22, 40]. Therefore, the real role of tenofovir in the clinical evolution of COVID-19 remains uncertain and needs to be better understood.

Given these inconsistencies, a systematic review of randomized controlled trials (RCTs) is necessary to clarify the clinical role of tenofovir in COVID-19. This review aims to synthesize the available evidence and assess whether tenofovir confers clinical benefits for patients with severe COVID-19.

Methods

Study design

This is a systematic review that involves searching for randomised controlled clinical trials to assess the efficacy of the drug of interest. The search, selection, data extraction and analysis of results were performed following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (version 6.2) [41] and described by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard [42]. The review protocol was registered in PROSPERO (CRD42023465336).

Search strategy

The search strategy was guided by the PICOS tool [43] (Table 1).

Studies investigating the efficacy of tenofovir on the clinical evolution of patients with COVID-19 were searched from six electronic databases: MEDLINE, Scopus, Cochrane Library, LILACS, SciELO, and Coronavirus Disease 2019 Living Overview of the Evidence (COVID-19 L.OVE). The descriptors "tenofovir" and "COVID-19", as well as their related terms, were defined according to the Medical Subject Heading (MeSH), being combined using the Boolean operator "AND" and "OR". Details about the adaptation of search strategies according to the different electronic databases are presented in the Supplementary Material S1.

Searches were conducted without restrictions regarding language, publication date or geographic region. The last search was conducted on April 16, 2025.

Eligibility criteria

Randomized controlled clinical trials that used tenofovir as monotherapy or in combination for patients with a confirmed diagnosis of COVID-19 were included, regardless of the specific healthcare setting in which they were treated. Review articles, notes, emails, editorials, letters, papers presented at scientific meetings, and studies with unavailable access were excluded. In cases

Table 1 Acronym PICOS

Acronym	Definition
P	Population (adult patients– 18 years or older– with laboratory-confirmed diagnosis of COVID-19, with or without HIV infection)
I	Intervention (oral administration of tenofovir disoproxil fumarate or tenofovir alafenamide as monotherapy or in combination with other drugs)
C	Control (placebo administration or no exposure to tenofovir)
O	Outcome (primary outcome: mortality from COVID-19/ secondary outcomes: admission to the intensive care unit, mechanical ventilation support and length of stay)
S	Study (randomized controlled clinical trial)

where the original text was not available, the corresponding author was contacted via email up to 3 times, and studies that were not available after the last contact were excluded. Additionally, the following exclusion criteria were considered: (i) inconclusive COVID-19 diagnosis; (ii) COVID-19 diagnosis based only on the symptomatic (clinical) pattern; (iii) patients with COVID-19 and concomitant infection with other respiratory pathogen(s); (iv) lack of specific information about the study population and its outcomes.

Studies selection

The results of searches in electronic databases were compiled at the Rayyan Qatar Computing Research Institute [44]. The search and selection of studies were conducted by two independent researchers (TLSS and VMRG), according to the established inclusion and exclusion criteria. Initially, a preliminary reading of the title, abstract and keywords was performed to identify and pre-select the studies of interest. The pre-selected studies were then subjected to a complete reading to analyze their adequacy to the inclusion criteria. Additionally, the reference lists of the selected studies were screened to identify potential clinical trials for review. Discrepancies regarding the selection process were resolved by a third researcher.

Risk of bias

The risk of bias analysis was performed independently by two reviewers using the Risk of Bias 2 (RoB 2) tool developed by Cochrane for the analysis of randomized trials [45]. Discrepancies were resolved between reviewers by discussion.

Data extraction

The selected articles were subjected to an analytical reading to identify and extract the variables of interest: reference (first author; year of publication)/study design (methods; location; inclusion and exclusion criteria)/ characteristics of study participants (age; sex; number of participants)/outcomes associated with the severity of COVID-19 (mortality; admission to the intensive care unit; mechanical ventilation support; length of stay).

Results

Search results

Initially, 1241 studies were retrieved by searching the six electronic databases. After excluding 313 duplicates, 928 titles and abstracts were screened. Finally, eight records were assessed for eligibility, of which four were excluded for involving patients without a confirmed diagnosis of COVID-19 [46–49], and one was excluded because lacking outcomes of interest [35, 50]. Therefore, three randomized clinical trials were eligible for inclusion in this systematic review (Fig. 1). No additional articles were retrieved from the reference lists of the included studies or via other methods.

Notably, the limited number of randomized clinical trials included in the systematic review, as well as the substantial heterogeneity identified among them, precluded the use of statistical methods for quantitative data synthesis, rendering a meta-analysis unfeasible. Therefore, a qualitative analysis was conducted, with a critical synthesis of the available evidence.

Study and patients characteristics

The selected clinical trials were developed in Colombia, Spain and Iran and published in 2022, 2023 and 2024, respectively [51–53]. Patient recruitment took place in 32 hospitals. Although the Colombian and Iranian trials included only hospitalized patients, the Spanish trial was conducted predominantly with hospitalized individuals ($n = 344$), but also included a small number of participants from outpatient settings ($n = 7$) and long-term care facilities ($n = 4$) [52]. In the Colombian and Spanish trials, tenofovir disoproxil was administered in a combined antiretroviral regimen with emtricitabine. The dosage of tenofovir disoproxil ranged from 200 mg to 300 mg per day (oral route) for 10 to 14 days, and patients were monitored until discharge or death. In the Iranian trial, tenofovir alafenamide was administered at a dose of 25 mg/day (oral route) for seven days, and patients were followed until the completion of treatment. The main studies characteristics are described in Table 2.

A total of 1048 patients with confirmed COVID-19 were included, with a predominance of male and notable differences in age to the intervention groups: mean of 53.6 years in the tenofovir disoproxil/emtricitabine + colchicine + rosuvastatin arm *versus* 56.6 years in the tenofovir disoproxil/emtricitabine arm of the Colombian study [51, 52], median of 68.0 years in the Spanish study [52] and mean of 61.3 years in the Iranian study [53]. The pre-existing comorbidities that stood out most in the three studies were diabetes and hypertension [51–53], while

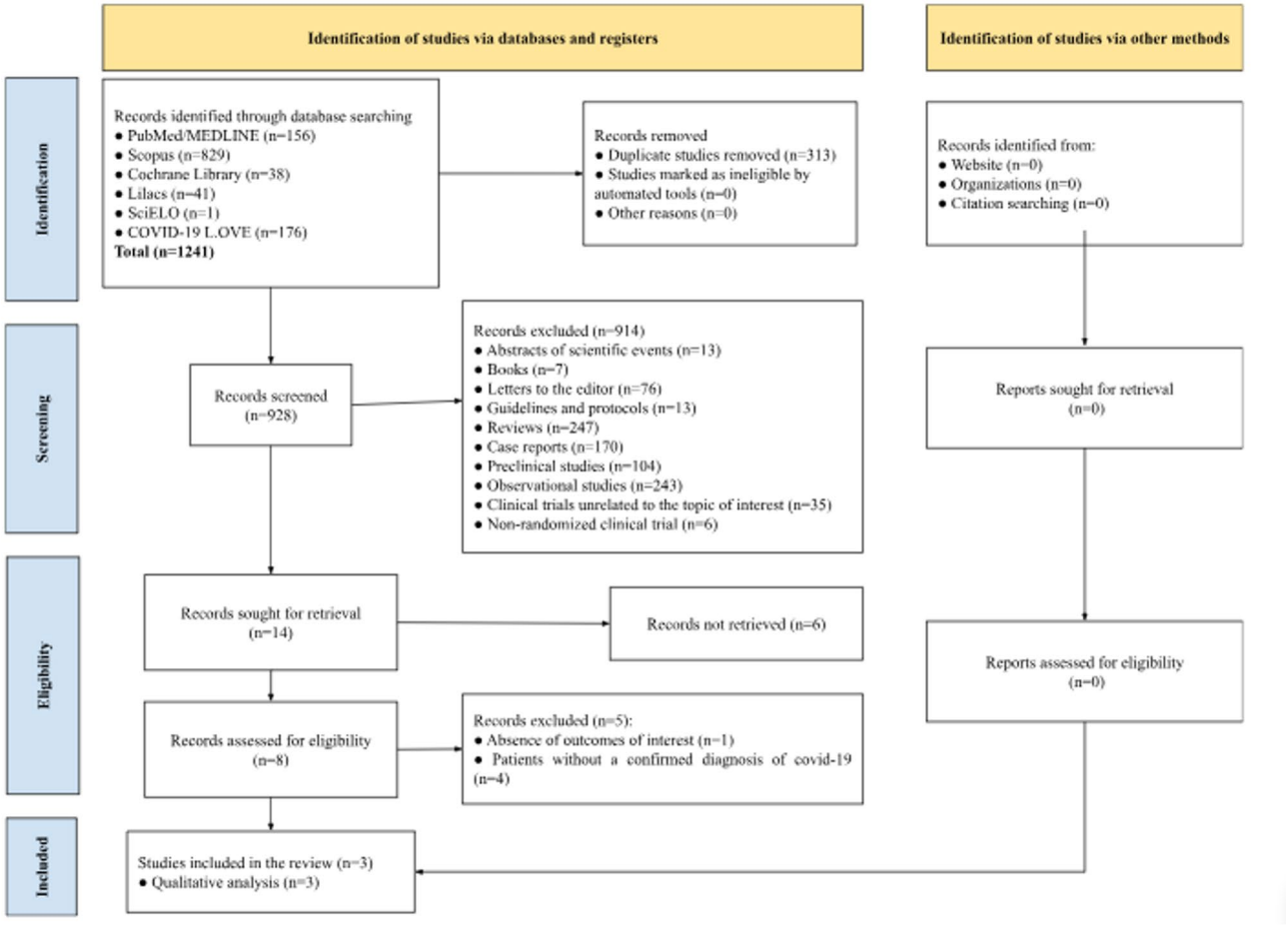

Fig. 1 Representative flowchart of the search process for identifying and selecting studies for the systematic review (Adapted from the Preferred Reporting Items for Systematic Review and Meta-Analyses - PRISMA flowchart model). Source: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 doi: https://doi.org/10.1136/bmj.n71

obesity was more frequent in the studies conducted in Colombia and Spain [51, 52] (Table 3).

Risk of bias

The study developed by Montejano et al. (2023) [52] was classified as having a low risk of bias, whereas concerns were identified in the study developed by Gaitán-Duarte et al. (2022) [51], especially regarding the randomization process (Supplementary Material S2). Baseline imbalances between intervention groups contributed to potential bias, and the open-label design led to a considerable rate of non-adherence (18.0–25.0%), increasing the risk of performance bias [51]. The study by Pouri et al. (2024), in turn, demonstrated a high risk of bias due to the lack of description of co-interventions administered during patient follow-up and the absence of a predefined statistical analysis plan for outcome assessment [53].

Efficacy results

The trials yielded conflicting results regarding the efficacy of tenofovir in COVID-19 treatment. The Colombian clinical trial [51], demonstrate that the combination of tenofovir disoproxil/emtricitabine when associated with colchicine and rosuvastatin was effective in reducing 28-day mortality (hazard ratio [HR] = 0.53; 95% CI: 0.29 to 0.96). This treatment was able to reduce mortality in 28 days, in cases of mild to moderate COVID-19 (RD = −0.05; 95% CI: −0.07 to −0.04). Furthermore, there was a lower need for invasive mechanical ventilation when compared to the control group (RD = −0.08; 95% CI: −0.11 to −0.04). However, the authors reported that tenofovir disoproxil/emtricitabine alone did not demonstrate a significant impact on the evaluated outcomes (Table 3). It is noted that patients allocated to the tenofovir disoproxi/emtricitabine treatment group presented important differences when compared to patients treated with tenofovir disoproxil/emtricitabine + colchicine + rosuvastatin. In this case, even when considering the analyses adjusted for age, sex and severity of pneumonia, it was not possible to observe efficacy for treatment with tenofovir disoproxi/emtricitabine (HR: 0.605; 95% CI: 0.343 to 1.065). Additionally, no adjustments were made

Table 2 Main characteristics of the studies included in the analysis

Reference	Register	Country	Blinding	Intervention	Control	Place of recruitment	Recruitment period	COVID-19 diagnostic method	COVID-19 severity	Exclusion criteria
Gaitán-Duarte et al., 2022 [51]	NCT04359095	Colombia	Open-label	Three intervention arms: 1- tenofovir disoproxil with emtricitabine (300/200 mg PO for 10 days); 2- colchicine plus rosuvastatin (0.5 mg and 40 mg PO for 14 days); 3- tenofovir disoproxil with emtricitabine plus colchicine and rosuvastatin at the same dose and during the same time period	(SoC) based on the recommendations of the Colombian consensus for hospitalized patients with COVID-19 that includes the use of dexamethasone, ivermectin or albendazole as prophylaxis for *Strongyloides* infection, enoxaparin, acetaminophen, oxygen as needed, and mechanical ventilation, or dialysis, if required.	6 hospitals in Bogotá	August, 2020 to March, 2021	RT-PCR or antigenic test	Mild, moderate or severe*	Pregnant women; patients taking any of the study drugs within the last 7 days; patients with known allergies to any of the drugs; patients with a history of myopathy, rhabdomyolysis, liver or renal failure or lung fibrosis; patients with advanced or metastatic cancer; and patients with a score greater than 3 on the frailty scale.

Table 2 (continued)

Reference	Register	Country	Blinding	Intervention	Control	Place of recruitment	Recruitment period	COVID-19 diagnostic method	COVID-19 severity	Exclusion criteria
Montejano et al., 2023 [52]	EudraCT 2020-001156-18	Spain	Open-label	Receive or not receive tenofovir disoproxil with emtricitabine (200/245 mg) (2 oral tablets on the first day and 1 tablet daily for a total of 14 days). Baricitinib plus dexamethasone or dexamethasone alone (4 mg once a day for 10–14 days, at the discretion of the investigator. For patients aged > 75 years, the dose of baricitinib was reduced to 2 mg once a day. The dosing for dexamethasone was 6 mg daily (oral or intravenously) for 7–10 days.	None of the medications of intervention	25 hospitals, led by La Paz University Hospital	October, 2020 to September, 2021	RT-PCR or antigenic test	Not disclosed	Main exclusion criteria were creatinine clearance < 60 mL/minute, receiving steroids at immunosuppressive doses (≥ 15 mg/day in the 7 days prior to the onset of symptoms), HIV infection, and severe respiratory failure (requiring a reservoir bag, mechanical ventilation, or acute respiratory distress) at the time of inclusion.

Table 2 (continued)

Reference	Register	Country	Blinding	Intervention	Control	Place of recruitment	Recruitment period	COVID-19 diagnostic method	COVID-19 severity	Exclusion criteria
POURI et al., 2024 [53]	IRCT20200422047168N1	Iran	Open-label	Tenofovir (25 mg) and normal therapy including remdesivir with corticosteroids (orally daily for 7 days).	Normal therapy including remdesivir with corticosteroids (orally daily for 7 days).	Hospital Razi in Ahvaz	September, 2020 to February, 2021	RT-PCR	Moderate or severe**	Pregnant or breast-feeding women; individuals who were vaccinated during this period; individuals prior diagnosis of renal failure; individuals with documented allergies to any of the medications, individuals those taking medications that interact with tenofovir; individuals requiring mechanical ventilation; individuals who left the hospital or expressed a desire to leave the study at any point during the study; participants who had previously taken part in other clinical trials.

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; COVID-19: coronavirus disease 2019; HIV: human immunodeficiency virus; PO; Per os; RT-PCR: Reverse transcription-polymerase chain reaction; SoC: Standard of care* Mild pneumonia was defined based on chest X-ray findings plus 2 or more risk factors for COVID-19 complications, including age over 60 years, pre-existing cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease (COPD), or cancer. Moderate pneumonia was defined based on X-ray findings, such as, bilateral air-space consolidation, usually ground glass opacities with peripheral and basal distribution, in accordance with local guidelines and hospitalization criteria on the simplified severity scale (CRB-65) > 1 or ambient oxygen saturation under 90%. Severe pneumonia was defined using the same criteria as for moderate pneumonia plus any of the following: respiratory rate of more than 30 breaths per minute; or the need for mechanical ventilation (invasive or non-invasive); or sepsis identified by a score of 2 or more on the Sequential Organ Failure Assessment (SOFA) scale; or 2 out of 3 of a Glasgow score of 13 or less, systolic blood pressure of 100 mmHg or less, and respiratory rate of 22 breaths per minute or higher; or a diagnosis of septic shock or multiple organ failure or adult respiratory distress syndrome** Moderate individuals were defined based on signs of lower respiratory illness during clinical evaluation or imaging and oxygen saturation (SpO2) of 94% or higher when breathing normal air at sea level. Severe individuals were defined based on blood oxygen saturation (SpO2) levels below 94% while breathing normal air at sea level, a ratio of arterial partial pressure of oxygen to the fraction of inspired oxygen (PaO2/FiO2) below 300 mm Hg, a respiratory rate over 30 breaths per minute, or lung infiltrates covering more than 50% of the lung area

for pre-existing comorbidities, and patients allocated to this group had a greater number of comorbidities such as cardiovascular disease (5.6%), diabetes mellitus (13.1%), chronic respiratory disease (5.6%) and cancer (5.6%).

Conversely, the Spanish clinical trial did not demonstrate efficacy for tenofovir disoproxil/emtricitabine in reducing 28-day mortality (risk ratio [RR] = 1.76; 95% CI: 0.52 to 5.91) or for the composite outcome of intensive care unit admission, disease progression, and 28-day mortality (RR = 0.95; 95% CI: 0.66 to 1.40) (Table 3). In this study, the randomization process was stratified by age group, duration of symptoms and hospital site, ensuring a balanced distribution of patient characteristics across groups. However, the absence of adjusted models limited the analytical power in evaluating efficacy outcomes.

The Iranian clinical trial [53], aimed at evaluating tenofovir alafenamide in combination with standard treatment (remdesivir and corticosteroids), demonstrated a significant reduction in the need for mechanical ventilation (0.0% vs. 13.3%, $p = 0.038$) and in ICU length of stay (3.3 days vs. 14.5 days; $p = 0.04$). However, critical aspects regarding the study's methodology limit this finding, given that the co-interventions that could have artificially favored the intervention group were not accounted for, and adjustments for potential confounding factors were not performed.

Regarding the safety assessment, the Colombian and Spanish [51, 52] studies demonstrated the occurrence of adverse events among patients allocated to the intervention groups. In the Colombian study [51], non-serious adverse events were more frequent and included gastrointestinal manifestations ($n = 88$), hepatic manifestations with elevated transaminases, alkaline phosphatase, and bilirubin levels ($n = 67$), as well as nonspecific conditions such as asthenia, cramps, and diaphoresis ($n = 23$). Serious adverse events were less common, with one case of generalized rash reported in the tenofovir disoproxil/emtricitabine group, one case of severe diarrhea in the tenofovir disoproxil/emtricitabine group associated with colchicine and rosuvastatin, and another case of severe diarrhea in the colchicine and rosuvastatin group. In the Spanish study [52], the most common adverse events among patients taking tenofovir disoproxil/emtricitabine were hyperglycemia ($n = 7$), elevated transaminases ($n = 5$), diarrhea ($n = 7$), and constipation ($n = 4$). Additionally, seven patients experienced serious adverse events. In the Iranian study [53], no serious adverse events or outcomes related to tenofovir alafenamide toxicity were reported during the follow-up period. However, the small sample size hinders the detection of less frequent adverse events.

Discussion

The systematic literature search revealed conflicting evidence regarding the efficacy of tenofovir in the clinical outcomes of COVID-19. Only three randomized clinical trials were retrieved, and their divergent findings on mortality, ICU admission, mechanical ventilation, and hospital length of stay make it difficult to draw definitive conclusions.

The Colombian trial [51] demonstrated a significant reduction in adverse clinical outcomes with the combination of tenofovir disoproxil/emtricitabine + colchicine + rosuvastatin compared to the control. However, this study presented concerns regarding the risk of bias, as the intervention groups exhibited imbalances in baseline characteristics such as age, sex, and comorbidities. While adjustments for age, sex, and pneumonia severity were made, further analyses incorporating pre-existing comorbidities are essential to strengthen the interpretation of efficacy results. Additionally, non-adherence rates of 18.0–25.0% were observed, which could have influenced the study outcomes. In this regard, the perception that the drug is no longer necessary due to an improvement in the clinical condition, as well as the perception that the drug has no effect or that it causes adverse events, are crucial factors for non-adherence among participants in clinical trials, which can compromise the efficacy results regarding the treatments under analysis [54]. Another important aspect concerns the sample size ($n = 633$), since the previously calculated ideal sample ($n = 816$) could not be achieved due to high refusal rate (33.0%) and exclusion of patients on chronic statins (38.0%). This specific condition may have resulted in imprecise estimates, with wide 95% confidence intervals [54–56]. Taken together, these described limitations raise concerns about the potential overestimation of the reported benefits and highlight the need for cautious interpretation.

In addition, it is noted that the observed efficacy in the Colombian study for tenofovir disoproxil/emtricitabine + colchicine + rosuvastatin, but not for tenofovir disoproxil/emtricitabine alone, reinforces the importance of careful interpretation [51]. More recent evidence indicates that neither colchicine nor statins have demonstrated significant clinical benefits in COVID-19 [57, 58]. Therefore, it is not possible to clearly attribute the effect to tenofovir, and other factors, such as methodological biases and differences in patient characteristics, may have influenced the results. Finally, it should be considered that the clinical trial in question was conducted with funding from pharmaceutical industries, which may introduce potential conflicts of interest. While industry funding does not necessarily compromise the integrity of a study, it is essential to critically assess aspects such as study design, data analysis, and interpretation of results

Table 3 Main results and outcomes of interest

Reference	Patients included									
	Age (years) [a, b]		Male sex, *n* (%) [c]		Patients, *n*		Comorbidities, *n* (%)		Severity of COVID-19, *n* (%)	Clinical outcomes
	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention		
Gaitán-Duarte et al., 2022 [51]	55.3 (± 12.3)	Tenofovir/emtricitabine: 56.6 (± 13.1) Colchicine + rosuvastatin: 56.1 (± 13.2) Tenofovir/emtricitabine + colchicine + rosuvastatin: 53.6 (± 12.6)	113 (70.2%)	Tenofovir/emtricitabine: 100 (62.5%) Colchicine + rosuvastatin: 103 (67.3%) Tenofovir/emtricitabine + colchicine + rosuvastatin: 112 (70.4%)	161	Tenofovir/emtricitabine: 160 Colchicine + rosuvastatin: 153 Tenofovir/emtricitabine + colchicine + rosuvastatin: 159	Obesity: 45 (30.2%) Hypertension:29 (18.0%) Diabetes: 12 (7.5%)	Tenofovir/emtricitabine: obesity: 58 (38.2%) hypertension: 46 (28.7%) diabetes: 21 (13.1%) Colchicine + rosuvastatin: obesity: 48 (34.0%) hypertension: 51 (33.3%) diabetes: 24 (15.7%) Tenofovir/emtricitabine + colchicine + rosuvastatin: obesity: 58 (39.2%) hypertension: 50 (31.4%) diabetes: 19 (11.9%)	Mild: 45 (7.0%) Moderate: 25 (67.0%) Severe: 163 (26.0%)	● 28-day mortality was significantly lower among patients treated with tenofovir disoproxil/emtricitabine + colchicine + rosuvastatin compared with the control group (HR = 0.53; 95% CI: 0.29 to 0.96). ● When considering the severity pattern, 28-day mortality was lower among patients treated with tenofovir disoproxil/emtricitabine + colchicine + rosuvastatin compared with the control group in cases of mild to moderate COVID-19 (HR = −0.05; 95% CI: −0.07 to −0.04). ● The need for invasive mechanical ventilation was lower among patients treated with tenofovir disoproxil/emtricitabine + colchicine + rosuvastatin compared with the control group (RD = −0.08; 95% CI: −0.11 to −0.04). ● There was no significant difference in mean length of hospital stay for any of the treatment groups under study. ● There was no significant difference in mortality, need for mechanical ventilation, or mean length of hospital stay for patients treated with tenofovir disoproxil/emtricitabine alone.

Table 3 (continued)

Reference	Patients included									
	Age (years) [a, b]		Male sex, *n* (%) [c]		Patients, *n*		Comorbidities, *n* (%)		Severity of COVID-19, *n* (%)	Clinical outcomes
	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention		
Montejano et al., 2023 [52]	67.0 (62.2–73.0)	68.0 (62.0–74.0)	116 (65.2%)	113 (63.8%)	178	177	Hypertension: 105 (59.0) Diabetes: 45 (25.3) Obesity: 30 (16.9)	Hypertension: 112 (63.3) Diabetes: 52 (29.4) Obesity: 27 (15.3)	Not disclosed	● There was no significant difference in 28-day mortality between patients treated with tenofovir disoproxil/emtricitabine compared to the control group (RR = 1.76; 95% CI: 0.52 to 5.91). ● There was no significant difference in the combined outcome of intensive care unit admission, disease progression, and 28-day mortality (RR = 0.95; 95% CI: 0.66 to 1.40) or in the other secondary outcomes in any of the treatment groups under study.
POURI et al., 2024 [53]	60.03 (±18.03)[a]	61.33 (±13,09)[a]	15 (50.0%)	16 (53.3%)	30	30	Hypertension: 12 (40%) Diabetes: 11 (36.7%)	Hypertension: 10 (33.3%) Diabetes: 14 (46.7%)	Not disclosed	● Patients in the intervention group had a mean (±SD) ICU stay of 3.33 (±0.57) days, whereas those in the control group stayed for an average of 14.5 (±6.85) days. This disparity in the length of ICU admission reflected statistical significance (p-value = 0.04). ● All 4 patients from the control group who were admitted to the ICU experienced severe respiratory distress, evidenced by symptoms such as dyspnea, oxygen saturation falling below 93%, and elevated PCO2 levels, necessitating mechanical ventilation. This occurrence was found to be statistically significant (p-value = 0.038). ● No patient died during the study.

[a]Value represented by mean and standard deviation. [b]Value represented by median and interquartile range. [c]Male sex. SoC: Standard of care; CI: Confidence interval; COVID-19: coronavirus disease 2019; HR: Hazard ratio; ICU: Intensive care unit; PCO2: Partial pressure of carbon dioxide; PO: per os; RD: risk difference; RR: risk ratio; SD: Standard deviation

to ensure transparency and minimize biases. Independent replication of findings in studies without industry sponsorship would be valuable in strengthening the evidence regarding the efficacy of tenofovir in COVID-19 treatment [59].

In contrast, the Spanish study [51, 52] had a lower risk of bias and did not demonstrate a significant effect of tenofovir disoproxil/emtricitabine on the outcomes of interest. The results were imprecise, with wide confidence intervals, which may be attributed to a small sample size ($n = 355$), making the study underpowered. The low overall mortality (3.1%) further limited statistical power, as over 5,000 patients per group would be needed to detect a significant reduction in mortality. Additionally, the study's initial sample size calculation assumed a 20% mortality rate and a 30% risk reduction, which may have led to an overestimation of the expected effect. The 4.8% ($n = 17$) loss to follow-up could also have influenced the final analysis [52]. Moreover, the absence of adjusted analyses in this study may reduce the certainty of the reported results. Given these limitations, the findings remain inconclusive, aligning with previous discussions on statistical power in clinical trials [59, 60].

The Iranian study [53], whose results indicated a significant reduction in the need for mechanical ventilation and ICU length of stay with the use of tenofovir alafenamide, demonstrated a high risk of bias. The absence of description of co-interventions and of a predefined statistical analysis plan substantially limits the interpretation and generalizability of the findings. Consequently, the lack of data regarding co-interventions raises uncertainties about the true attribution of the outcomes to the intervention under analysis, given that these results may be associated with other concomitant clinical decisions that could be influenced by awareness of the assigned study group by healthcare personal. Furthermore, the absence of a predefined specification of the statistical analyses to be applied to the primary outcomes expands the possibility of eligibility of analyses, with preferential presentation of the most favorable results, thus representing a potential selective reporting bias. The small number of participants ($n = 60$) in the Iranian study reflects a low statistical power, which limits the ability to detect true differences between groups, increases the risk of type II errors, and compromises the precision of effect estimates, potentially leading to overestimation of results [61, 62]. The absence of prior sample size calculation and the lack of adjusted analyses for potential confounding factors also contribute to the statistical fragility of the findings, preventing assertive definition regarding the efficacy of tenofovir in modulating the outcomes under analysis. In this regard, although this clinical trial presented promising results, a conservative interpretation is warranted.

In general, although tenofovir based regimens are generally associated with an acceptable safety profile in the clinical practice, the trials included in this review did not demonstrate meaningful clinical benefit in the context of COVID-19. The available safety data were not sufficiently detailed or harmonized across studies to allow a comprehensive risk-benefit analysis. Therefore, given the absence of demonstrated efficacy and the potential for adverse events, even if infrequent, there is currently no evidence-based justification to recommend tenofovir for COVID-19 treatment.

In addition, it is noted that tenofovir is a drug used in the treatment of people living with HIV, and the inclusion of HIV-positive patients in studies can act as a confounding factor in the results. While the Spanish study clearly states that HIV-positive patients would be excluded [52], the other studies do not mention this criterion and do not provide information on the patients' HIV status in the demographic data [51, 53], which could contribute to heterogeneity between studies. It should also be emphasized that among the studies included in this review, important differences were identified regarding the clinical treatment settings of the patients. While the Colombian and Iranian trials exclusively enrolled hospitalized patients, the Spanish trial, although predominantly conducted in hospital settings ($n = 344$), also included patients treated in outpatient clinics ($n = 7$) and long-term care facilities ($n = 4$). This contextual variability is relevant, as clinical outcomes such as mortality and the need for mechanical ventilation may be significantly influenced by the treatment setting. Evidence shows that hospitalized patients with COVID-19 tend to present with higher severity and, consequently, a greater risk of adverse outcomes when compared to those treated in outpatient or residential settings, particularly among older adults and those with chronic conditions such as hypertension, diabetes, or cardiovascular disease [63–65].

According to current World Health Organization guidelines [6], standard therapy for hospitalized patients includes antivirals such as remdesivir for those who do not require mechanical ventilation, corticosteroids such as dexamethasone, immunomodulators such as baricitinib or tocilizumab, and anticoagulation—particularly with low molecular weight heparin—for patients at risk of thromboembolic events. In the case of outpatients with mild to moderate COVID-19 who are at increased risk of progression to severe disease, the use of oral antivirals such as nirmatrelvir/ritonavir is recommended, and, in selected cases, molnupiravir. Additionally, remdesivir may also be administered intravenously in specific cases where hospitalization is not required. These recommendations are based on high-certainty evidence derived from randomized clinical trials with substantial methodological robustness [6].

In this context, it is evident that tenofovir is not included among the therapeutic options recommended for the treatment of COVID-19, whether in outpatient or inpatient settings, due to the lack of consistent scientific evidence supporting its efficacy in the clinical management of the disease. Thus, the limited and conflicting evidence available on tenofovir, including the findings synthesized in our review, does not support its inclusion in treatment protocols. This reinforces our cautious conclusion that tenofovir cannot be recommended for the treatment of COVID-19, particularly considering the availability of more well-established therapeutic alternatives.

At the time of this review, no other systematic reviews had been identified that focused on randomized clinical trials investigating tenofovir's impact on COVID-19 outcomes. However, systematic reviews and meta-analyses of observational studies have suggested a potential association between tenofovir use and reduced COVID-19 complications [66, 67]. Nevertheless, observational studies are inherently prone to biases, such as confounding and selection bias, which can limit the reliability of their findings. Given these methodological constraints, randomized controlled trials remain essential to establish a causal relationship between tenofovir use and clinical outcomes in COVID-19 patients. However, given the current stage of the pandemic and the availability of more established treatments, conducting new randomized clinical trials on tenofovir for COVID-19 is unlikely.

This systematic review has some limitations. The inclusion of only three studies reflects the scarcity of randomized clinical trials on this topic. In addition, only one clinical trial adjusted the analysis to the level for COVID-19 severity [51], which is a crucial factor in treatment response interpretation. Another relevant condition that may have influenced the results found is the absence of analyses of tenofovir as monotherapy since the three clinical trials evaluated tenofovir in combination with other drugs. Despite these constraints, the rigorous methodology employed in this review enhances its reliability by minimizing bias through systematic literature selection, data extraction, and analysis. Furthermore, this review provides a clear framework for assessing study quality, strengthening the overall evidence base and identifying gaps for future research.

Conclusions

This systematic review does not provide sufficient evidence to support the use of tenofovir for the treatment of COVID-19 patients. The limited number of randomized clinical trials, their methodological constraints, and potential biases prevent definitive conclusions regarding its efficacy. Although some observational studies have suggested an association between tenofovir use and reduced COVID-19 complications, their inherent limitations make it impossible to establish a causal relationship. Given the current stage of the pandemic and the availability of more established treatments, conducting new randomized clinical trials on tenofovir for COVID-19 is unlikely. Therefore, based on the inconclusive evidence synthesized in this review and considering the current COVID-19 treatment guidelines, tenofovir should not be recommended for the management of the disease.

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
FDA	Food and Drug Administration
HR	Hazard ratio
ICU	Intensive care unit
LILACS	Latin American and Caribbean Health Sciences Literature
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	Medical Subject Heading
PCO2	Partial pressure of carbon dioxide
PO	Per os
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RCT	Randomized controlled trial
RD	Risk difference
RdRp	RNA-dependent RNA polymerase
RNA	Ribonucleic acid
RoB	Risk of bias
RR	Risk ratio
RT-PCR	Reverse transcription-polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SciELO	Scientific Electronic Library Online
SD	Standard deviation
SoC	Standard of care
SOFA	Sequential Organ Failure Assessment

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Data availability
All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

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The authors declare no competing interests.

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