BOGOMOLETS NATIONAL MEDICAL UNIVERSITY
FACULTY OF PHARMACY
DEPART. OF CLINICAL PHARMACOLOGY AND CLINICAL PHARMACY

Theme of graduation qualification work:

CLINICAL AND PHARMACOLOGICAL FEATURES OF THE INTERACTION OF TENOFOVIR AND ENTECAVIR WITH ANTI-ARRHYTHMIC DRUGS

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We would like to thank God for his mercy and grace, and we hope that God will accept this work with good acceptance.

We would like to express our sincere gratitude, thanks and great appreciation for our supervisor for his valuable and helpful advice and suggestions he provided and for our assistance and all her efforts made to complete this research

Alfuraiji Hawraa

Dedication

To those who lit the first light in my life…..

To those who exerted the effort of years in generosity, and make from days stairs for me to rise…..

my mother and my father.

To everyone whom taught us anything ever, our teachers.

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List of Abbreviations

Ab-	Meaning
CAST	Cardiac Arrhythmia Suppression Trial
ETV	entecavir
HF	heart failure
IV	intravenously
MI	myocardial infarction
VF	ventricular fibrillation
VT	ventricular tachycardia

3.3 Potassium channel blockers

Chapter one

Introduction

1.1 Relevance of the problem

1.2 Chronic hepatitis B (CHB) remains a significant global health issue. [1].

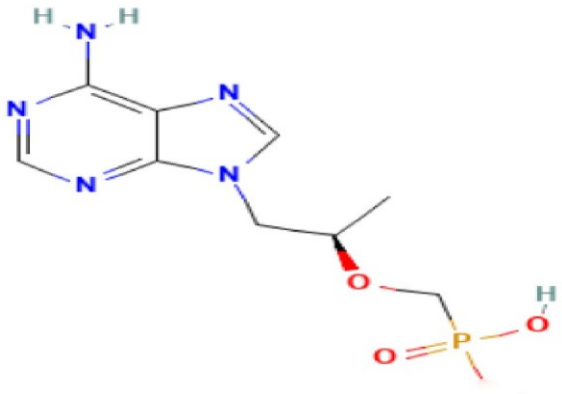
1.3 These medications are known for effectively reducing hepatitis B virus (HBV) levels in the body. However, since TAF is relatively new, it hasn't yet been incorporated into some clinical guidelines, such as those for acute-on-chronic liver failure (ACLF) [2].

1.4 Tenofovir

1.4.1. Description:

Tenofovir (Fig. 1) (anhydrous) is phosphonic acids. An inhibitor of HIV-1 reverse transcriptase, the bis (isopropyloxycarbonyloxymethyl) ester (disoproxil ester) prodrug is used as the fumaric acid salt in the therapy of HIV. It is a member of phosphonic acids and a nucleoside analogue. It is a conjugate acid of a tenofovir [3].

Fig.1: Structure of tenofovir.



1.4.2. Mechanism of Action:

Tenofovir, once activated in the body through phosphorylation, interferes with the virus's ability to replicate. It mimics a DNA building block, getting incorporated into the virus's genetic material and causing the replication process to fail. This mechanism is highly efficient and safe, thanks to its low interaction with the host's own DNA enzymes [4].

1.4.3. Absorption, Distribution and Excretion:

1.4.3.1Absorption:

The raw form of tenofovir isn't well absorbed when taken by mouth. To improve its effectiveness, it's delivered in prodrug forms like TDF or TAF. This is due to its molecular structure, which carries electrical charges that make it difficult to pass through cell membranes. As a result, oral absorption is poor, while intravenous administration achieves higher blood levels [5].

1.4.3.2Route of Elimination

Once in the system, tenofovir is primarily excreted through the kidneys. Both glomerular filtration and active tubular secretion help remove the drug, with transport proteins such as organic anion transporters (OAT1 and OAT3) and multidrug resistance-associated protein 4 (MRP4) playing key roles [6].

1.4.3.3Volume of Distribution

Its volume of distribution is about 0.813 L/kg, and elevated plasma concentrations are associated with potential kidney toxicity [7].

1.4.3.4**Clearance**

Clearance depends on kidney function: people with normal renal function eliminate it at about 210 mL/min, while those with impaired function may clear it at a slower rate, around 134 mL/min [8].

1.4.4. Metabolism / Metabolites

Inside liver cells, tenofovir undergoes two phosphorylation steps to become tenofovir diphosphate, the active form responsible for stopping HBV replication [9].

1.4.5. FDA Pharmacological Classification:

Tabel 1: FDA Pharmacological Classification.

3.3 Potassium channel blockers

FDA UNII	W4HFE001U5
Active Moiety	TENOFOVIR ANHYDROUS
Pharmaco-	EPC – HIV
logical Classes	Nucleoside Analog Reverse Transcriptase Inhibitor
Pharmaco-	EPC – HBV Nucleoside Analog
logical Classes	Reverse Transcriptase Inhibitor
Pharmaco-	Chemical Structure [CS] - Nucleosides
Pharmaco-	MoA - Nucleoside Inhibitors
FDA Phar-	
macology Summary	Tenofovir anhydrous is a HIV and HBV Inhibitor.

1.2.6 Pharmacodynamics:

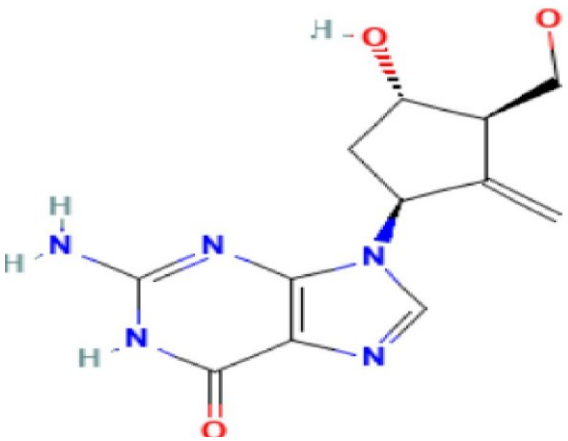
Tenofovir has demonstrated strong antiviral activity, particularly in patients new to antiretroviral therapy. It performs comparably to efavirenz and is generally better tolerated than older drugs like stavudine. In HBV-infected individuals, viral DNA often becomes undetectable after one year of treatment [10].

1.5 Entecavir

1.5.1. Description:

Entecavir is another key antiviral agent used for CHB. It is a synthetic version of a guanosine analogue and acts by inhibiting the viral enzyme necessary for DNA synthesis. Once phosphorylated in cells, it competes with natural DNA components, halting the virus's replication process [11].

Fig.2: Structure of entecavir.



Mechanism of Action:

Entecavir blocks multiple stages of the HBV polymerase activity: it prevents the enzyme from starting DNA synthesis, copying the negative strand, and creating the positive strand. It does this by imitating the normal building blocks the virus uses. Importantly, entecavir is selective and does not inhibit HIV [12].

Although it is a potent antiviral, entecavir shows low activity against human DNA polymerases, reducing the risk of side effects. The binding affinity (Ki) for host enzymes is relatively weak, ranging from 18 to over 160 micromolar [13].

1.5.2. Absorption, Distribution and Excretion:

1.5.2.1**Absorption:**

1.5.2.2Following oral intake, entecavir is rapidly absorbed, with peak blood levels reached within 0.5 to 1.5 hours. When taken on an empty stomach, its absorption is optimal, showing 100% bioavailability compared to the liquid formulation [14].

1.5.2.3Distribution:

1.5.2.4Food can delay absorption and reduce peak levels by around 44% to 46%, and total exposure (AUC) by about 18% to 20%. Despite this, the drug is still widely distributed in tissues and only lightly binds to blood proteins (about 13%). Steady-state drug levels are typically achieved after 6 to 10 days of daily dosing, with roughly a two-fold buildup. Renal clearance ranges between 360 and 471 mL/min and involves both filtration and secretion [15]. Animal studies have found entecavir in breast milk, but human data is lacking [16].

3.3 Potassium channel blockers

1.5.3. Clearance:

1.5.4. Kidney function greatly influences how quickly the drug is cleared:

1.5.5. Normal renal function: renal clearance ~383.2 mL/min; oral clearance ~588.1 mL/min

1.5.6. Mild impairment: renal clearance ~197.9 mL/min; oral clearance ~309.2 mL/min

1.5.7. Moderate impairment: renal clearance ~135.6 mL/min; oral clearance ~226.3 mL/min

1.5.8. Severe impairment: renal clearance ~40.3 mL/min; oral clearance ~100.6 mL/min

1.5.9. On hemodialysis: oral clearance ~50.6 mL/min

1.5.10. On CAPD: oral clearance ~35.7 mL/min [17]

1.5.11.Metabolism / Metabolites:

1.5.12. Very little of entecavir is metabolized. It does not produce oxidative or acetylated byproducts, and only minor amounts of glucuronide and sulfate conjugates are detected. It's not affected by the cytochrome P450 system, which means fewer drug interactions [18].

1.5.13.FDA Pharmacological Classification:

Tabel 2: FDA Pharmacological Classification of entecavir.

FDA UNII	**NNU2O4609D**
Active Moiety	ENTECAVIR ANHYDROUS
Pharmacological Classes	EPC - HBV
Pharmacolog-	Nucleoside Analog
Pharmacolog-	MoA
FDA Pharmacology Summary	Entecavir is HBV Inhibitor.
Non-Proprie-	ENTECAVIR

Pharmacological Classes	MoA – HBV Reverse Transcriptase Inhibitor

1.5.14. Pharmacodynamics

1.6 Entecavir efficiently blocks all three phases of the hepatitis B replication cycle, making it a powerful treatment. It is even more effective than older drugs like lamivudine [19].

1.7 Antiarrhythmic Drugs

Moving beyond hepatitis B, antiarrhythmic drugs are used to treat abnormal heart rhythms. They're classified based on where they act in the electrical cycle of the heart. Choosing the right drug depends on the arrhythmia type, other conditions the patient may have, and possible side effects [20].

1.7.1. Arrhythmias—abnormal heartbeats—are quite common and can cause anything from minor discomfort to life-threatening events. They may arise on their own or as a result of other conditions. Managing arrhythmias often involves medications to correct the rhythm or control the heart rate [21].

1.7.2. Classification of arrhythmias:

Arrhythmias are usually classified by where they begin in the heart. Supraventricular arrhythmias originate in the atria or AV node, while ventricular arrhythmias start below the AV node. Fast heart rhythms are known as tachyarrhythmias (over 100 bpm), and slow rhythms are bradyarrhythmias (under 60 bpm). Tachyarrhythmias are often treated with medications, while bradyarrhythmias may need a pacemaker. In emergencies, drugs like atropine can raise heart rate temporarily [22][23].

TABEL 4: CHARACTERISTICS OF SUPRAVENTRICULAR AND VENTRICULAR ARRHYTHMIAS

Arrhythmias	Morphology	Considerations

3.3 Potassium channel blockers

Tachycardia	Regular, wide QRS	Managed with or without cardioversion depending on stability
Torsades de pointes	Twisting QRS pattern	Often due to electrolyte imbalances or prolonged QT.
Ventricular fibril-lation	Chaotic, disorganized activity	Requires immediate defib-rillation.

To manage these conditions, the Vaughan Williams classification organizes drugs by how they affect the cardiac action potential [24].

Tabel 5: The classification of the antiarrhythmic therapy.

- I class (sodium channel blockers):
  - Ia (intermediate action): quinidine, procainamide
  - Ib (fast action): lidocaine, mexiletine
  - Ic (slow action): flecainide, propafenone
- II class: Slow heart rate and reduce oxygen demand (e.g., bi-soprolol, carvedilol)
- III class: Prolong repolarization.
- IV class.
- Class V (other): Digoxin and adenosine, which work through different mechanisms

1.4.2.1 Class I agents – sodium-channel blockers

Mechanism of I class antiarrhythmics block sodium channels in cardiac cells. They differ in how quickly they attach and detach from the sodium channel:

- Ia drugs (e.g., procainamide) act at a moderate rate
- Ib drugs (e.g., lidocaine) are the fastest
- Ic drugs (e.g., flecainide) are the slowest [26]

This structure helps tailor treatment based on the arrhythmia type.

Indications.

Ia class. Procainamide, when used, is typically reserved for managing both ventricular and supraventricular tachycardias and can be given orally, intramuscularly, or intravenously. However, it carries a risk of inducing a lupus-like autoimmune syndrome in many patients [27]. Quinidine, on the other hand, is sometimes employed to prevent ventricular arrhythmias, particularly in Brugada syndrome or idiopathic ventricular fibrillation (VF). It can cause nausea, stomach cramps, and increase the risk of digitalis toxicity. Additionally, because it prolongs the QT interval, quinidine has also been used for treating short QT syndrome [27].

1.4.2.2 Class Ib Agents Lidocaine is widely known as a local anesthetic, often used via injection. When given intravenously, however, it serves as a Class Ib antiarrhythmic and is effective in treating ventricular tachycardia. Side effects can include symptoms of nervous system activation or suppression, slowed heart rate, arrhythmias, and low blood pressure [28].

1.4.2.3 **Class Ic Agents**

Flecainide is often used in a "pill-in-the-pocket" approach for managing sudden-onset atrial fibrillation (AF) [29]. However, this class of drugs is not safe for patients who have had a heart attack or experienced life-threatening arrhythmias, due to the risk of inducing dangerous ventricular tachycardia or cardiogenic shock. This was highlighted by the CAST trial, which found a higher death rate among post-MI patients treated with flecainide or encainide compared to those given a placebo [30].

1.4.2.4 **II class.**

Biological means of action initiation:

3.3 Potassium channel blockers

Beta-blockers exert their pharmacodynamic effects by competitively antagonizing beta-adrenergic receptors, thereby attenuating downstream signaling pathways associated with sympathetic nervous system activation. This leads to a reduction in chronotropic and inotropic cardiac responses, ultimately promoting rhythm stabilization and decreased myocardial workload.

They are divided into cardioselective (targeting the heart) and non-cardioselective types [31].

Clinical indications:

Clinical Uses These medications are used to manage fast heart rhythms like atrial fibrillation and flutter. They are also helpful in heart failure, after a heart attack, for glaucoma, and in treating symptoms like anxiety and tremor [32].

Contraindications and Side Effects Beta-blockers are not advised for people with asthma, although those with COPD may tolerate them. Other conditions to watch for include advanced heart block. Common side effects are tiredness and sleep problems; using hydrophilic beta-blockers like atenolol can help prevent sleep disturbances [33].

2 **Table 6: Clinical and Pharmacological Features of Beta-blockers [5, 6]**

Agent	Day Dose	Frequency	Half-life (h)	Nature	Cardioselectivity
Atenolol	50 mg	2	7	Hydrophilic	Cardioselective
Bisoprolol	5-10 mg	1	11	Lipophilic	Cardioselective
Carvedilol	10-25	2	10	Lipophilic	Non-cardioselective
Labetalol	100–200 mg	2	5	Lipophilic	Non-cardioselective

Metoprolol	100 mg	3	4	Lipophilic	Cardioselective
Proprano-lol	20 mg	3	4	Lipophilic	Non-cardioselec-tive
Sotalol	100 mg	2	15	Hydro-philic	Non-cardioselec-tive

2.4.2.1 **III class agents.**

Mechanism of action:

Potassium channels play a pivotal role in cardiac repolarization by facilitating the outward movement of potassium ions, thereby enabling propagation of the cardiac action potential. Pharmacological inhibition of these channels impedes potassium efflux, resulting in delayed repolarization. This delay manifests as a prolongation of both the action potential duration (APD) and the effective refractory period (ERP), ultimately leading to slowed myocardial conduction. Clinically, these electrophysiological alterations appear as QT interval prolongation on the electrocardiogram (ECG).

III class, particularly amiodarone, sotalol, and dronedarone, are most frequently employed for their potassium channel-blocking properties. However, their pharmacodynamic profiles are not limited to pure class III activity. Amiodarone exhibits a broad spectrum of effects, incorporating elements of class I (sodium channel blockade), class II (beta-adrenergic antagonism), and class IV (calcium channel blockade). Sotalol combines class III action with non-selective beta-blocking (class II) effects, while dronedarone demonstrates a mixed profile with activity across all four Vaughan Williams classes (I–IV) [34].

Clinical Uses. Sotalol is also used for arrhythmias but lacks safety data for use in heart failure [35].

Warnings and Side Effects:

People with an already prolonged QT interval are at risk of developing dangerous arrhythmias if treated with these drugs. Sotalol should be avoided in patients with heart failure, kidney issues, or low potassium. Amiodarone, while effective, has

3.3 Potassium channel blockers

a long list of potential adverse effects, especially when used long-term (over six months). About 1% of users per year experience serious side effects, including lung damage, thyroid issues, photosensitivity, skin discoloration, corneal deposits, nerve damage, and liver problems. Regular monitoring of thyroid and liver function is advised every six months [36][37][38].

2.4.2.2 **IV class**

2.4.2.3 **Mechanism of effectivness:**

Verapamil and diltiazem block calcium entry into heart cells. This slows AV node conduction and reduces contractility. These drugs are distinct from dihydropyridines (e.g., amlodipine), which are primarily used to lower blood pressure and don't affect heart rhythm [39].

Clinical Uses:

These drugs are mainly used to prevent or treat supraventricular tachycardias. They're a good alternative when beta-blockers aren't suitable, such as in patients with lung issues. However, combining them with beta-blockers or quinidine should be avoided due to risk of severe bradycardia or asystole.

Side Effects

2.4.2.4These medications lower heart strength, so they are not recommended for people with heart failure. Side effects can include slow heart rate, AV block, dizziness, flushing, and headaches. Verapamil can also cause constipation, skin rashes, and nausea [40].

V class.

Digoxin An old remedy with roots going back to 1785, digoxin slows the heart by enhancing vagal tone. It's mainly used for rate control in AF and atrial flutter. While it doesn't stop arrhythmias, it can help manage the heart rate. Digoxin's effects can be boosted by other drugs like quinidine and amiodarone or by low potassium levels. However, it can also cause serious rhythm issues, especially in overdose. This medication is not recommended for use in patients with heart block and it should be administered with caution in elderly individuals or those with impaired renal function [41, 42].

Adenosine This drug is a natural compound formed in the body and works by slowing conduction through the AV node via specific potassium and calcium channel actions. It is given as a quick IV push for treating supraventricular tachycardias and has a very short half-life (under 10 seconds). Common side effects include flushing, chest discomfort, and a sensation of impending doom. Because it can trigger bronchospasm, it should not be used in asthmatics [43][44].

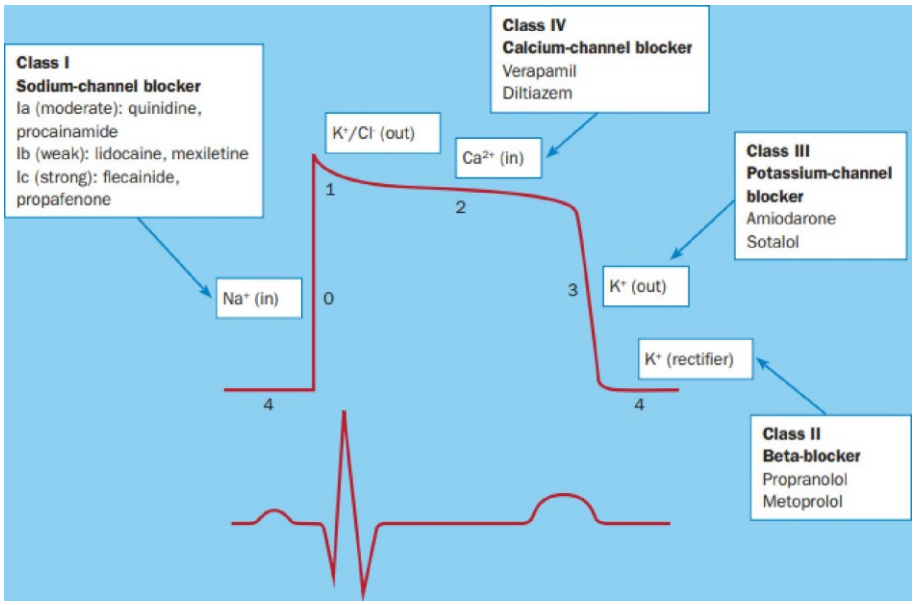


Fig.3: Medications influencing the cardiac action potential.

THE RESEARCH METHODS AND MATERIALS USED IN THE WORK

2.1. Justification of research methods and objects

After reviewing theoretical sources and statistical data on the prevalence of chronic hepatitis B (CHB) and associated comorbidities requiring the use of both cardiotropic and antiviral drugs, the need to assess the safety of their combined use became evident. In recent years, not only infectious disease specialists and gastroenterologists, but also physicians from other specialties have become actively involved in the treatment of CHB.

3.3 Potassium channel blockers

Entecavir is generally well tolerated and causes relatively few adverse reactions, especially when compared to Tenofovir. This often creates a false sense of safety for both doctors and patients, leading them to underestimate the risks of potential drug interactions during comorbid therapy. As a result, serious side effects may occur due to unmonitored drug combinations.

Given the importance of this issue, we conducted an analysis of drug interactions between Entecavir and Tenofovir with major groups of antiarrhythmic agents. For this purpose, we used the “DrugBank” and “Hep Drug Interactions” databases to generate interaction protocols for each drug combination.

The main objectives of the study were as follows:

To identify the most common combinations of CHB drugs (Tenofovir and Entecavir) with cardiotropic agents, including antiarrhythmics, sodium channel blockers, beta-blockers, calcium channel blockers, and potassium channel blockers;

To analyze how frequently potentially harmful or unsafe combinations are prescribed in clinical practice when treating CHB patients with cardiovascular comorbidities;

To develop relatively safe combination schemes for the co-administration of Tenofovir or Entecavir with cardiotropic drugs in CHB therapy.

This research made it possible to address the main objectives outlined at the beginning of the master’s thesis.

Methods and Materials Used in the Study

2.1 Rationale for Research Design and Focus

To properly explore the issue, we first reviewed collected data on the prevalence of chronic hepatitis B (CHB) and related conditions that require simultaneous treatment with heart-acting (cardiotropic) and anti-HBV medications. As the treat-

ment of CHB has expanded beyond infectious disease specialists and gastroenterologists to include physicians from various disciplines, it has become especially important to understand potential drug interactions.

Entecavir tends to cause very few side effects, unlike Tenofovir, which can lead to the false impression among both patients and clinicians that it is entirely safe—an assumption that may ignore the risks posed when other conditions are present. This oversight could result in dangerous complications.

To address this concern, our study analyzed how Tenofovir and Entecavir interact with various classes of antiarrhythmic drugs. This analysis was conducted using two key online resources: "Drug Bank" and "Hep Drug Interactions." Based on these interactions, we created reference protocols for each drug combination. We also:

- Identified the most commonly prescribed combinations of Tenofovir or Entecavir with drugs from the following cardiotropic classes: sodium channel blockers, beta-blockers, calcium channel blockers, and potassium channel blockers.
- Analyzed how often physicians prescribe potentially unsafe or high-risk combinations.
- Proposed treatment regimens that allow for safer use of Tenofovir or Entecavir in patients with CHB who also require cardiotropic therapy.

By following these steps, the study addressed the main research questions posed at the outset of this master's thesis.

3.3 Potassium channel blockers

Chapter 2

Results

3. Interaction of tenofovir and entecavir with antiarrhythmic drugs

3.1 Class I agents – sodium-channel blockers

3.1.1 Class Ia agents – sodium-channel blockers:

Quinidine:

We analyzed drug-drug interactions between Quinidine (an antiarrhythmic drug) which block Na+ channel (intermediate association/dissociation) and K+ channel blocking effect and prolong the action potential and has an intermediate effect on the 0 phase of depolarization with tenofovir and entecavir.

It was established, that the concomitant use of Quinidine and Entecavir has

26 December 2023

A clinically relevant interaction is not expected while Tenofovir alafenamide + Quinidine has Potential clinically significant interaction.

Report ID:

Date Produced:

Hepatology Treatment	**Co-medications**
Entecavir	**Quinidine**
Tenofovir alafenamide	

This report lists the summaries of potential interactions (i.e. "red", "amber" and “yellow” classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hepatology-druginteractions.org .

Description of the interactions

Potential clinically significant interaction - likely to require additional monitoring, alteration of drug dosage or timing of administration (AMBER)

Tenofovir alafenamide + Quinidine

Quinidine is metabolised by CYP3A4. Tenofovir alafenamide (the prodrug of tenofovir) is a substrate of P-gp are expected to increase the absorption of tenofovir alafenamide and thereby increase the systemic concentration. Monitoring of tenofovir-associated adverse reactions is recommended.

A clinically relevant interaction is not expected (GREEN)

Entecavir + Quinidine

Disopyramide:

It was established, that the concomitant use of Disopyramide + Entecavir and Tenofovir alafenamide + Disopyramide has A clinically relevant interaction is not expected.

www.hepatology-druginteractions.org

Interaction Report

Report ID:

Date Produced: 26 December 2023

Hepatology Treatment	Co - medications
Entecavir	Disopyramide
Tenofovir alafenamide	

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

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For full details of all interactions, see www.hepatology-druginteractions.org .

Description of the interactions

3.3 Potassium channel blockers

A clinically relevant interaction is not expected (GREEN)

Entecavir + Disopyramide

Tenofovir alafenamide + Disopyramide

3.1.2 Class Ib agents – sodium-channel blockers:

Lidocaine:

We analyzed drug-drug interactions between Lidocaine (an antiarrhythmic drug) which Na+ channel block (fast association/dissociation). Class Ib drugs shorten the action potential of myocardial cell and has a weak effect on the initiation of phase 0 of depolarization with tenofovir and entecavir.It was established, that the concomitant use of Lidocaine (Lignocaine) + Entecavir and Tenofovir alafenamide + Lidocaine (Lignocaine) has A clinically relevant interaction is not expected.

www.hepatology-druginteractions.org

Interaction Report

Report ID:

Date Produced: 26 December 2023

Hepatology Treatment	Co-medications
Entecavir	**Lidocaine (Lignocaine)**
Tenofovir alafenamide	

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hepatologv-druqinteractions.org

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Description of the interactions

A clinically relevant interaction is not expected (GREEN)

Entecavir + Lidocaine (Lignocaine)

Tenofovir alafenamide + Lidocaine (Lignocaine)

Mexiletine:

It was established, that the concomitant use of Mexiletine + Entecavir and Tenofovir alafenamide + Mexiletine has A clinically relevant interaction is not expected.

Hepatology Treatment	Co-medications
Entecavir Tenofovir alafenamide	Mexiletine

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hepatology-druginteractions.org .

Description of the interactions

A clinically relevant interaction is not expected (GREEN)

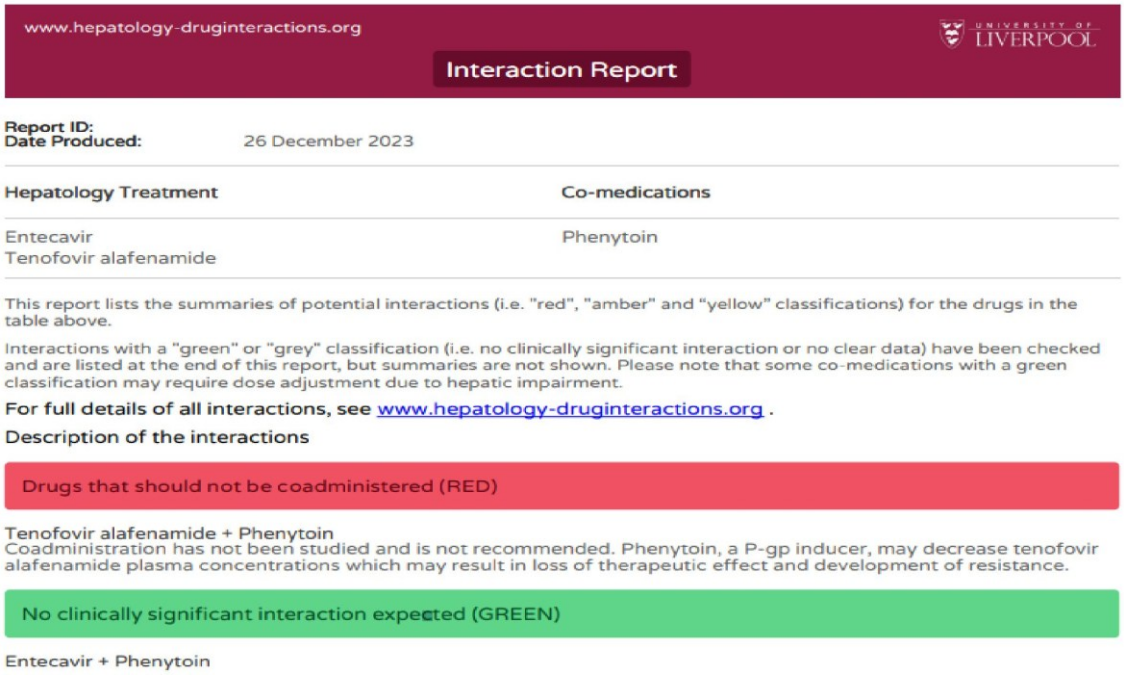
Entecavir + Mexiletine

Tenofovir alafenamide + Mexiletine

Phenytoin:

It was established, that the concomitant use of Phenytoin and Entecavir has A clinically relevant interaction is not expected while Tenofovir alafenamide + Phenytoin should not be coadministered.

3.3 Potassium channel blockers


www.hepatology-druginteractions.org

UNIVERSITY OF LIVERPOOL

Interaction Report

Report ID:
Date Produced: 26 December 2023

Hepatology Treatment	Co-medications
Entecavir Tenofovir alafenamide	Phenytoin

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

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For full details of all interactions, see www.hepatology-druginteractions.org .

Description of the interactions

Drugs that should not be coadministered (RED)

Tenofovir alafenamide + Phenytoin
Coadministration has not been studied and is not recommended. Phenytoin, a P-gp inducer, may decrease tenofovir alafenamide plasma concentrations which may result in loss of therapeutic effect and development of resistance.

No clinically significant interaction expected (GREEN)

Entecavir + Phenytoin

Flecainide:

It was established, that the concomitant use of Flecainide + Entecavir and Tenofovir alafenamide + Flecainide has A clinically relevant interaction is not expected.


www.hepatology-dru-

Interaction Report

Report ID:

Date Produced: 26 December 2023

Hepatology Treatment	Co-medications
Entecavir Tenofovir alafenamide	Flecainide

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hepatology-druqinteractions.org

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Description of the interactions

A clinically relevant interaction is not expected (GREEN)

Entecavir + Flecainide

Tenofovir alafenamide + Flecainide

Propafenone:

It was established, that the concomitant use of Propafenone + Entecavir and Tenofovir alafenamide + Propafenone has A clinically relevant interaction is not expected.

www.hepatology-druginteractions.org

Interaction Report

Report ID:

Date Produced: 26 December 2023

Hepatology Treatment	**Co-medications**
Entecavir	**Propafenone**
Tenofovir alafenamide	

This report lists the summaries of potential interactions (i.e. "red", "amber" and “yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hepatologv-druginteractions.org

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Description of the interactions

A clinically relevant interaction is not expected (GREEN)

Entecavir + Propafenone

Atenolol:

3.3 Potassium channel blockers

It was established, that the concomitant use of Atenolol + Entecavir and Tenofovir alafenamide + Atenolol has A clinically relevant interaction is not expected.

www.hepatology-druginteractions.org **Interaction Report**

Report ID:

Date Produced: 26 De-

Hepatology Treatment	**Co-medications**
Entecavir	**Atenolol**

This report lists the summaries of potential interactions (i.e. "red", "amber" and “yellow” classifications) for the drugs in the table above.

Interactions with a “green” or ’’grey” classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hepatology-druginteractions.org .

Description of the interactions

A clinically relevant interaction is not expected (GREEN)

Entecavir + Atenolol

Tenofovir alafenamide + Atenolol

Bisoprolol:

It was established, that the concomitant use of Bisoprolol + Entecavir and Tenofovir alafenamide + Bisoprolol has A clinically relevant interaction is not expected.

www.hepatology-druginteractions.org Interaction Report

Report ID:

Date Produced: 26 De-

Hepatology Treatment	Co-medica-
Entecavir Tenofovir alafenamide	Bisoprolol

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hepatologv-druginteractions.org .

Description of the interactions

A clinically relevant interaction is not expected (GREEN)

Entecavir + Bisoprolol

It was established, that the concomitant use of Carvedilol + Entecavir and Tenofovir alafenamide + Carvedilol has A clinically relevant interaction is not expected.

Hepatology Treatment	Co-medica- tions
Entecavir Tenofovir alafenamide	Carvedilol

This report lists the summaries of potential interactions (i.e. "red", "amber" and “yellow” classifications) for the drugs in the table above.

3.3 Potassium channel blockers

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hepatology-druginteractions.org

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Description of the interactions

A clinically relevant interaction is not expected (GREEN)

Entecavir + Carvedilol

Tenofovir alafenamide + Carvedilol

Metoprolol:

It was established, that the concomitant use of Metoprolol + Entecavir and Tenofovir

alafenamide + Metoprolol has A clinically relevant interaction is not expected.

www.hepatology-druginteractions.org

Interaction Report

Report ID:

Date Produced: 26 December 2023

Hepatology Treatment	**Co-medications**
Entecavir	**Metoprolol**
Tenofovir alafenamide	

This report lists the summaries of potential interactions (i.e. "red", "amber" and “yellow” classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hepatology-druginteractions.org

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Description of the interactions

A clinically relevant interaction is not expected (GREEN)

Entecavir + Metoprolol

It was established, that the concomitant use of Nebivolol + Entecavir and Tenofoviralafenamide + Nebivolol has A clinically relevant interaction is not expected.

Report ID:

Date Produced: 26 December 2023

Hepatology Treatment	Co-medications
Entecavir	Nebivolol
Tenofovir alafenamide	

This report lists the summaries of potential interactions (i.e. "red", "amber" and “yellow” classifications) for the drugs in the table above.

Interactions with a "green" or "grey” classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hepatologv-druqinteractions.org

Description of the interactions

A clinically relevant interaction is not expected (GREEN)

Entecavir + Nebivolol

Tenofovir alafenamide + Nebivolol

Propranolol:

It was established, that the concomitant use of Propranolol + Entecavir and Tenofovir alafenamide + Propranolol has A clinically relevant interaction is not expected.

3.3 Potassium channel blockers

Interaction Report

Report ID:

Date Produced: 26 December 2023

Hepatology Treatment	**Co-medications**
Entecavir	**Propranolol**
Tenofovir alafenamide	

This report lists the summaries of potential interactions (i.e. "red", "amber" and “yellow” classifications) for the drugs in the table above.

Interactions with a "green” or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hepatologv-druginteractions.org

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Description of the interactions

A clinically relevant interaction is not expected (GREEN)

Entecavir + Propranolol

Timolol:

It was established, that the concomitant use of Timolol + Entecavir and Tenofovir alafenamide + Timolol has A clinically relevant interaction is not expected.

www.hepatology-druginteractions.org Interaction Report

Report ID:

Date Produced: 26 De-

Hepatology Treatment	Co-medica-
Entecavir	Timolol
Tenofovir alafenamide	

This report lists the summaries of potential interactions {i.e. "red", "amber" and “yellow” classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hepatoloqy-druginteractions.org .

Description of the interactions

A clinically relevant interaction is not expected (GREEN)

Entecavir + Timolol

Tenofovir alafenamide + Timolol

Amiodarone:

It was established, that the concomitant use of Amiodarone and Entecavir has A clinically relevant interaction is not expected while Tenofovir alafenamide + Amiodarone has Potential clinically significant interaction.

Report ID:

Date Produced: 26 December 2023

Hepatology Treatment	**Co-medications**
Entecavir	**Amiodarone**
Tenofovir alafenamide	

This report lists the summaries of potential interactions (i.e. "red", "amber" and “yellow” classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of

3.3 Potassium channel blockers

this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hepatology-druginteractions.org .

Description of the interactions

Potential clinically significant interaction - likely to require additional monitoring, alteration of drug dosage or timing of administration (AMBER)

Tenofovir alafenamide + Amiodarone

Amiodarone is metabolised by CYP3A4 and 2C8. Tenofovir alafenamide (the prodrug of tenofovir) is a substrate of P-gp is expected to increase the absorption of tenofovir alafenamide and thereby increase the systemic concentration. Monitoring of tenofovir- potential complications, necessitating ongoing assessment of kidney health, is recommended.

A clinically relevant interaction is not expected (GREEN)

Entecavir ♦ Amiodarone

Dofetilide:

It was established, that the concomitant use of Dofetilide + Entecavir and Tenofoviralafenamide + Dofetilide has A clinically relevant interaction is not expected.

www.hepatology-druginteractions.org

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Interaction Report

Report ID:
Date Produced: 26 December 2023

Hepatology Treatment	Co-medications
Entecavir Tenofovir alafenamide	Dofetilide

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hepatology-druginteractions.org .

Description of the interactions

No clinically significant interaction expected (GREEN)

Entecavir + Dofetilide

Tenofovir alafenamide + Dofetilide

3.4 Calcium channel blockers

Dronedarone:

It was established, that the concomitant use of Dronedarone + Entecavir and Tenofovir alafenamide + Dronedarone has A clinically relevant interaction is not expected.

Report ID:

Date Produced: 26 De-

Hepatology Treatment	Co-medica-
Entecavir Tenofovir alafenamide	Dronedarone

This report lists the summaries of potential interactions (i.e. "red", "amber" and “yellow” classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hepatologv-druqinteractions.org .

Description of the interactions

A clinically relevant interaction is not expected (GREEN)

Entecavir + Dronedarone

Tenofovir alafenamide + Dronedarone

Vernakalant:

It was established, that the concomitant use of Vernakalant + Entecavir and Tenofovir alafenamide + Vernakalant has A clinically relevant interaction is not expected.

3.5 others

Interaction Report

Report ID:

Date Produced: 26 December 2023

Hepatology Treatment	**Co-medications**
Entecavir	Vernakalant
Tenofovir alafenamide	

This report lists the summaries of potential interactions (i.e. "red", "amber" and “yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hepatologv-druqinteractions.org .

Description of the interactions

A clinically relevant interaction is not expected (GREEN)

Entecavir + Vernakalant

Tenofovir alafenamide + Vernakalant

Diltiazem:

It was established, that the concomitant use of Diltiazem + Entecavir and Tenofovir alafenamide + Diltiazem has A clinically relevant interaction is not expected.

www.hepatology-druginteractions.org **Interaction Report**

Report ID:

Date Produced: 26 December 2023

Hepatology Treatment	Co-medications
Entecavir	Diltiazem

3.5 others

Tenofovir alafenamide

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hepatology-druqinteractions.org .

Description of the interactions

A clinically relevant interaction is not expected (GREEN)

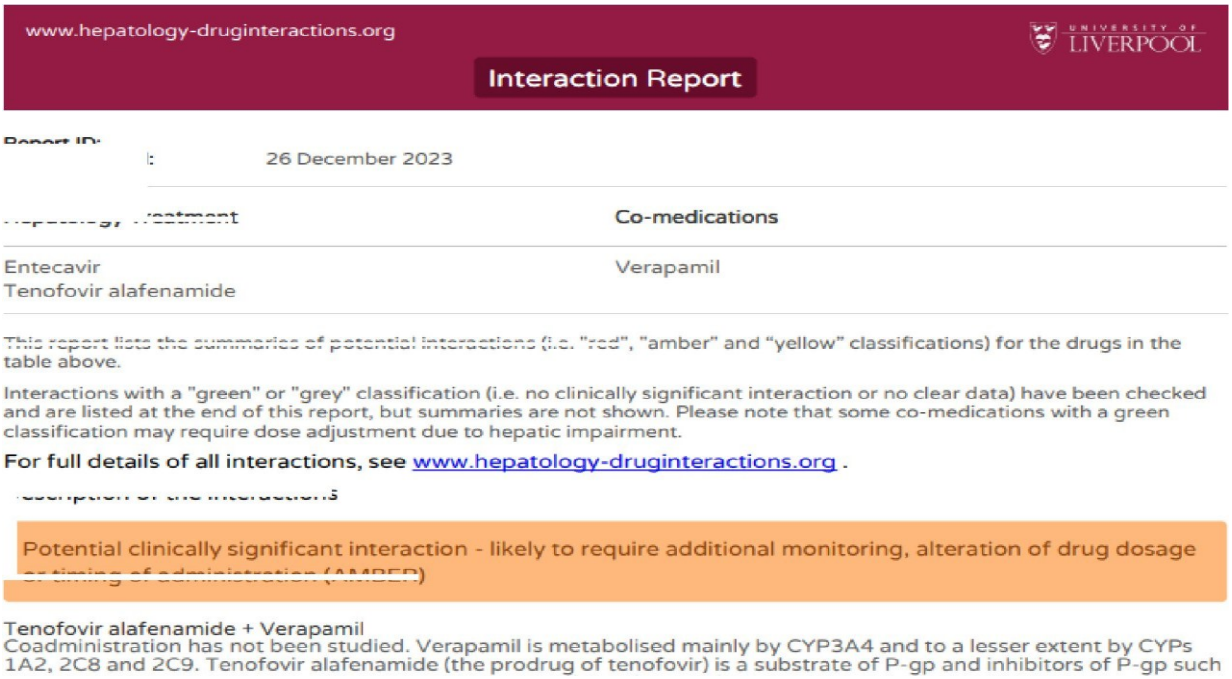
Entecavir + Diltiazem

Tenofovir alafenamide ♦ Diltiazem

Verapamil:

It was established, that the concomitant use of Verapamil and Entecavir has A clinically relevant interaction is not expected while Tenofovir alafenamide + Verapamil has Potential clinically significant interaction.

Report ID:


www.hepatology-druginteractions.org

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Interaction Report

26 December 2023

	Co-medications
Entecavir Tenofovir alafenamide	Verapamil

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hepatology-druginteractions.org .

Potential clinically significant interaction - likely to require additional monitoring, alteration of drug dosage

Tenofovir alafenamide + Verapamil

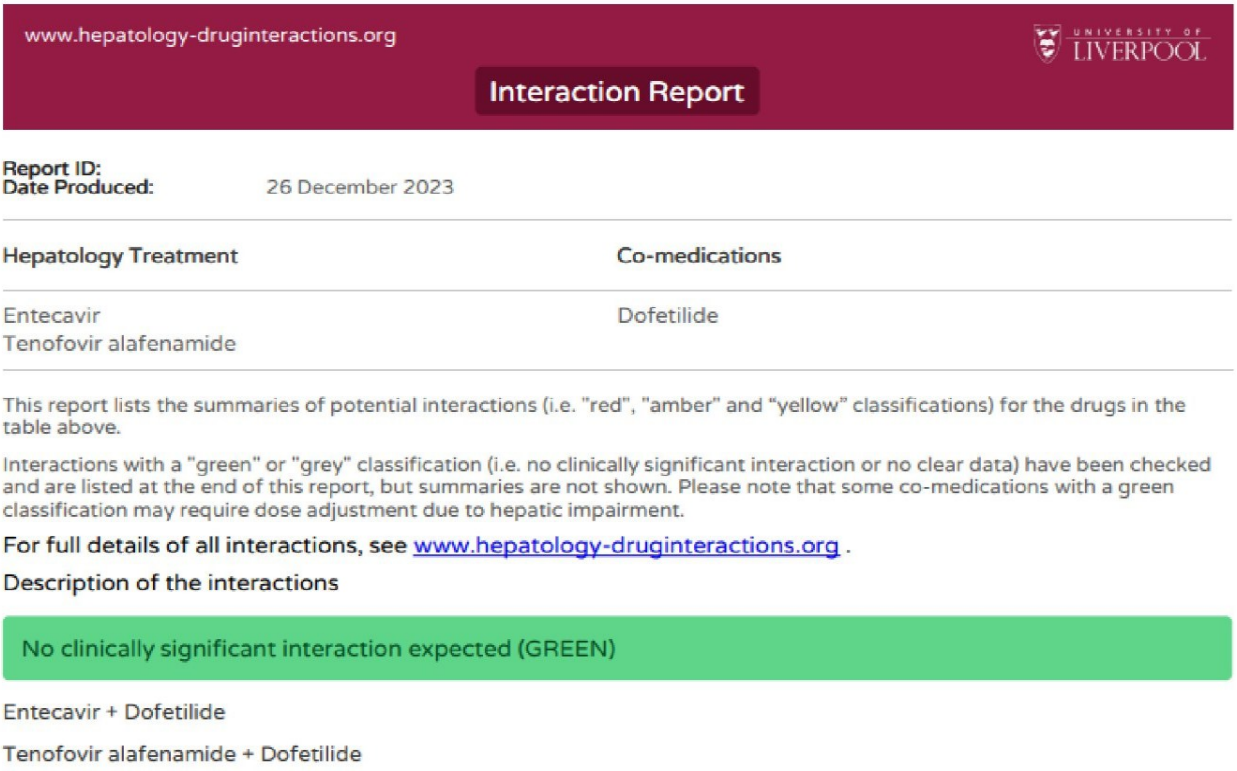
Coadministration has not been studied. Verapamil is metabolised mainly by CYP3A4 and to a lesser extent by CYPs 1A2, 2C8 and 2C9. Tenofovir alafenamide (the prodrug of tenofovir) is a substrate of P-gp and inhibitors of P-gp such

3.5 others

Date Produced:

Description of the interactions

No clinically signficant interaction expected (GREEN)



www.hepatology-druginteractions.org

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Interaction Report

Report ID:
Date Produced: 26 December 2023

Hepatology Treatment	Co-medications
Entecavir Tenofovir alafenamide	Dofetilide

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hepatology-druginteractions.org .

Description of the interactions

No clinically significant interaction expected (GREEN)

Entecavir + Dofetilide

Tenofovir alafenamide + Dofetilide

3.5 others

Digoxin:

It was established, that the concomitant use of Digoxin + Entecavir and Tenofovir

alafenamide + Digoxin has A clinically relevant interaction is not expected.

Report ID: Date Produced:

Hepatology Treatment	Co-medications
Entecavir	Digoxin
Tenofovir alafenamide	

This report lists the summaries of potential interactions (i.e. "red", "amber" and “yellow” classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hepatologv-druqinteractions.org .

Description of the interactions

A clinically relevant interaction is not expected (GREEN)

Entecavir + Digoxin

Tenofovir alafenamide + Digoxin

Chapter 3

Conclusion and References

4.1 Conclusion

1 We analyzed drug-drug interactions between sodium-channel blockers with tenofovir and entecavir It was established, that sodium-channel blockers with Entecavir has no clinically significant interaction and also sodium-channel blockers with Tenofovir alafenamide has no clinically significant interaction except Tenofovir alafenamide + Quinidine has Potential clinically significant interaction, Tenofovir alafenamide + Phenytoin should not be Coad ministered.

2 We analyzed drug-drug interactions between Beta-blockers with tenofovir and entecavir It was established, that beta-blockers with Entecavir and Tenofovir alafenamide has no clinically significant interaction.

3 We analyzed drug-drug interactions between Potassium channel blockers with tenofovir and entecavir It was established, that Potassium channel blockers with Entecavir and Tenofovir alafenamide has no clinically significant interaction except Tenofovir alafenamide + Amiodarone has Potential clinically significant interaction.

4 We analyzed drug-drug interactions between Calcium channel blockers with tenofovir and entecavir It was established, that Calcium channel blockers with Entecavir and Tenofovir alafenamide has no clinically significant interaction except Tenofovir alafenamide + Verapamil has Potential clinically significant interaction.

5 We analyzed drug-drug interactions between Digoxin with tenofovir and entecavir It was established, that Digoxin with Entecavir and Tenofovir alafenamide has no clinically significant interaction.

6 We analyzed drug-drug interactions between antiarrhythmic drugs with entecavir It was established, that antiarrhythmic drugs with Entecavir has no clinically significant interaction.

The purpose of the study was a clinical and pharmaceutical analysis of possible adverse reactions when simultaneous administration of antiarrhythmic drugs and direct antiviral drugs for the treatment of CHB.