

TENOFOVIR AND EMTRICITABINE (TRUVADA)



"Auroch Leaping", Minoan Fresco, Bronze Age, 2nd Millennium B.C, Knossos, Crete.

Zeus was overjoyed when his son was born, he wanted him to be a great hero and protector of the mortals, however his wife Hera always loathed any of the offspring of her husband's - all too frequent - "liaisons". She would do everything in her power to hinder, and hopefully destroy them, and her loathing applied most especially to the great Heracles. When Heracles had grown to manhood, he was given the hand in marriage of Megara, the beautiful daughter of the king of Thebes, Creon. Heracles had many children with Megara, but then Hera in a rage of jealousy cast a powerful spell over him that sent

him into a paranoid rage. Thinking he was surrounded by enemies on all sides he slew all of his children. When he realized what he had done he was inconsolable and went to the Oracle of Delphi to seek a means of penance and atonement. The hero was ordered to go into the service of King Eurystheus of Mycenae, as a common slave. The evil and dishonorable King Eurystheus was in fact a protégé of Hera, and so it seems that Hera herself had malignly influenced the sacred Oracle! Hera ordered King Eurystheus, to send Heracles on a suicide mission. Eurystheus, in his extreme eagerness to please Hera, did better than that - he ordered Heracles to ten suicide missions - which he later, extended to twelve, by trickery that showed a sick genius for manipulating contract law, which would have made his fortune in a later era! And so it was that Heracles was condemned to his famous twelve labours.

King Eurystheus was stunned when Heracles returned to Mycenae having successfully completed the sixth "impossible" task he had assigned him; the slaying of the terrifying Stymphalian Birds. He thought to himself that for the seventh task, he must next send Heracles on an even more dangerous mission - the capture of the monstrous Cretan Bull, which Heracles would have to bring back alive to Mycenae. The Cretan Bull was no ordinary bull. It had been created by the powerful god of the sea, Poseidon. King Minos of Crete had prayed to Poseidon to provide him with a suitable victim to sacrifice to the gods, and Poseidon had responded by sending Minos the bull, a huge and powerful creature that required all of King Minos's army to control it! But the animal was such a magnificent beast, that Minos wanted to own it himself and so he substituted another bull in its place to sacrifice to Poseidon. Poseidon discovered the disrespectful deceit and decided to inflict a terrible punishment on King Minos - indeed he planned to kill two birds with the one stone! King Minos's wife, Pasiphae, had also been somewhat lackadaisical in her offerings to the goddess Aphrodite. Poseidon approached Aphrodite and together they came up with a horrific plan to destroy the good name of both Minos and his wife. Aphrodite cast a spell over Pasiphae inflicting her with an unnatural lust for the bull. Pasiphae enlisted the help of a certain Daedalus, who assisted her in slaking her deranged passion which regrettably led to a hybrid - species pregnancy, and later on the birth of the terrifying Minotaur, a creature with the body of a man and the head of a bull. King Minos was no genius, but he quickly reached the appropriate conclusions and banished his wife and imprisoned Daedalus, but not before he forced him to build an immense underground maze in which to imprison his shameful stepson. He could not bring himself to have the bull killed however and so he merely set it loose, free to roam and terrorize the Cretan countryside. As strong as the great Cretan Bull was however, Heracles was yet stronger. He subdued it, tied it up, and bought it back to Mycenae and presented it to an astonished King Eurystheus. The King though was so terrified of it that he let it loose into the countryside, where it created havoc in the region of Marathon, near Athens, where its reign of destruction would eventually be ended by the hero, Theseus.

Of all the animals that humanity has managed to domesticate, perhaps none have been so important to humanity than the humble cow! Its meat and milk has become one of the most important sources of food that sustains the Earth's immense Homo sapiens population. Cattle have contributed to the rise of civilizations, and their ability to convert what is to humans indigestible material into edible fats and proteins is one of the principle reasons that makes it such a remarkable and valuable animal. So important was the cow to ancient civilizations it was revered as a sacred religious symbol in many

cultures. In ancient Mesopotamia (modern day Iraq) the horns of the bulls were symbols of both royalty and divinity. In ancient Egypt several divine beings took the form of cattle, Hathor, the goddess of love and motherhood, and Apis the bull deity was worshipped in the region of Memphis. Mummified bulls have been found in their own sarcophagi by archeologists. Cows have been sacred animals, immensely revered, to Hindus since before recorded history.

But cattle were not always so docile and easily handled however. Just as all dogs alive today are actually far distant domesticated descendants of ferocious wild wolves, last remnants of the Ice Age, so it is with the humble domesticated cow - all are descendants of once ferocious beasts of the Pleistocene - the aurochs. It is thought that the auroch evolved around two million years ago in the region of what today is India. They slowly migrated eastward and reached Europe around 250,000 years ago. Aurochs were immense animals, standing at around two meters tall at the shoulder. The males were crowned with a fearsome pair of long forward pointing lyre-shaped horns, formidable weapons against any aggressor including prehistoric humans. Aurochs feature prominently in Neolithic cave paintings found in both France and Spain. It is thought that the process of domestication of these animals began around six to eight thousand years ago. It would have been quite a task to tame these immensely powerful animals. When the historical record opens in the second millennium B.C there is mention of aurochs in both Egyptian hieroglyphics and also in the Minoan civilization of Crete. Cretan bull worship was probably the origin of the legend of the minotaur. The cult of the bull on ancient Crete was vitally important. A famous fresco from the palace of Knossos shows athletes doing back-flips across an auroch's back - a feat requiring a good deal more skill and bravery than subsequent civilizations slaughtering domesticated bulls with weapons in arenas in the name of "entertainment". It was probably in the Roman gladiatorial arenas, that the origin of the modern day anachronistic "sport" of bull fighting in Spain had its origins. One of the most famous Greek myths concerning bulls, apart from that of Theseus and the Minotaur is seen in the labours of Heracles. For his seventh labour Heracles had to capture the Cretan bull alive - and in proper historical context, this did not mean the docile modern equivalent of a bull that we see today, but rather, a giant auroch of Cretan legend! Aurochs survived in the remote wild along-side their increasingly domesticated descendents up to surprisingly modern times, the last recorded auroch dying in Poland in 1627 - another noble human strike in the great Sixth extinction event of life on planet Earth. The domestication of the auroch has been so successful that modern day environmentalists now see the vast industrial scale cattle farming of today with its land clearance to support it, as an increasing threat to the world's biodiversity, and incredibly, by cattle production of methane, a significant greenhouse gas, a not insignificant contributor to global warming!

To modern day sensibilities, the Seventh Labour of Heracles seems a quite manageable task - until we look at it in terms of proper historical context - King Eurystheus was not sending Heracles to bring in a stray docile bull by its nose ring - but rather to bring in a wild giant auroch of Cretan legend - a somewhat more daunting prospect - a fatal outcome was assumed! And so it is today with infection by HIV. With the miraculous antiretroviral drugs at our disposal, this disease is now a far more manageable beast. Where once a fatal outcome was almost assured, today a life expectancy of more than 35 years is considered a realistic possibility for a young person diagnosed with HIV infection in Australia.

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Introduction

Combination antiretroviral therapy has revolutionized the management of HIV infection.

A life expectancy of **more than 35 years** is now realistic for a young person diagnosed with HIV infection in Australia. ⁴

Despite this success, antiretroviral regimens predictably fail in a proportion of patients.

Research therefore is ongoing to discover, develop and deliver newer antiretroviral drugs.

Human immunodeficiency virus (HIV) therapeutics is a highly complex and specialized field, and so only specialists with experience in HIV management should start or change antiretroviral therapy.

Emergency Physicians should be aware of the *basic* therapeutics of the antiretroviral agents as:

- Treatment may need to be initiated in the ED, after specialist ID consultation, for patients requiring post exposure prophylaxis.
- Patients may present to the ED with toxic side effects.

Currently initial antiretroviral therapy, involves **at least three drugs:**

Generally this will be:

- Two NRTIs

Plus either:

- An NNRTI

Or

- A PI

Or

- An integrase inhibitor

Two other classes of drugs (the fusion inhibitors and the entry inhibitors), and particular drugs of the PI class (tipranavir and darunavir) and the NNRTI class (etravirine), are currently reserved for use in resistant HIV infection or when patients are unable to tolerate standard therapy.

Tenofovir and **Emtricitabine** are both **antiretroviral** drugs of the nucleoside/nucleotide reverse transcriptase inhibitor (**NRTI**) class.

These agents are available as a fixed-dose combination product (e.g. in Australia as **Truvada**).

This document describes the dual NRTI therapeutic agent **Truvada**.

Chemistry

Tenofovir is a nucleotide **analogue of adenosine**

Emtricitabine is a nucleoside **analogue of cytidine**.

- Cytidine is a nucleoside molecule that is formed when cytosine is attached to a ribose ring

Classification

The classes of *antiretroviral* drugs include:

1. Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)

Examples include:

- **Tenofovir**
- **Emtricitabine**
- Azidothymidine (AZT)

2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Examples include:

- Etravirine

3. Protease inhibitors (PIs):

Examples include:

- Tipranavir
- Darunavir
- Saquinavir

4. Integrase inhibitors (also known as integrase strand transfer inhibitors):

Examples include:

- Raltegravir
- Dolutegravir
- Elvitegravir

5. The fusion inhibitors:

Examples include:

- Enfuvirtide

6. The entry inhibitors (or Chemokine receptor antagonists - CCR5 antagonists):

Examples include:

- Maraviroc

Preparation

Tablets:

- **Truvada:** tenofovir disoproxil fumarate 300 mg and emtricitabine 200 mg.

Mechanism of Action

Tenofovir is a nucleotide **analogue of adenosine** that inhibits HIV and Hepatitis B virus.

Emtricitabine is a nucleoside **analogue of cytidine**.

The active phosphorylated NRTI metabolites inhibit viral reverse transcriptase and viral DNA synthesis, thus preventing HIV replication.

The *specific* sites of action differs for each drug; and so these differences are exploited in various combination regimens.

Pharmacokinetics

Absorption:

- Tenofovir and Emtricitabine are administered orally.

Metabolism and excretion:

- Tenofovir is about 80 % eliminated in the kidneys by a combination of glomerular filtration and active tubular secretion.

About 20 % of tenofovir is metabolized.

- Emtricitabine is about 90 % eliminated in the kidneys by a combination of glomerular filtration and active tubular secretion

About 10 % of emtricitabine is metabolized

Pharmacodynamics

Tenofovir disoproxil fumarate in combination with emtricitabine have **synergistic** antiretroviral activity in vivo.

Indications

Truvada in combination with other antiretroviral drugs is used for:

- The treatment of HIV infection
- Post exposure prophylaxis for HIV infection.
 - ♥ These drugs do not guarantee protection from the HIV but they do significantly reduce the risk of transmission of HIV (by about 70%).
- Prophylaxis during pregnancy to prevent vertical transmission of HIV

Tenofovir is also used to treat chronic hepatitis B infection.

Contraindications/ Precautions

These include:

1. Patients with known hypersensitivity to tenofovir, tenofovir disoproxil fumarate, emtricitabine or any other components of the tablet.
2. Renal impairment
3. Note that **cross resistance** among certain reverse transcriptase inhibitors has been recognised.

Pregnancy

Tenofovir is a category B3 drug with respect to pregnancy.

Category B3 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Breast feeding

In Australia, breastfeeding is not recommended for HIV positive women because of the possibility of HIV transmission and because suitable formula milk is readily available.

Adverse Effects

For truvada these may include:

1. Non-specific constitutional symptoms:
 - Lethargy/ malaise
 - Headache
 - Insomnia
2. GIT upset
3. Liver impairment
4. Renal impairment
5. Allergic reactions
6. Dermatological hypersensitivity reactions.

Dosing

For post -exposure prophylaxis: ¹

- It is essential to seek expert advice from a physician experienced in the management of HIV or to consult local guidelines before initiating PEP against HIV infection.
- If PEP against HIV is indicated, it should be started **as soon as possible after exposure (ideally within 2 hours of the exposure)** and definitely within 72 hours.
- If it has been longer than 72 hours since the exposure, PEP may be offered in some circumstances with expert advice.

In general terms recommendations for PEP include a basic regimen of two nucleoside/nucleotide reverse transcriptase inhibitors for “lower-risk” HIV exposures, and an expanded regimen (with the addition of a third drug) for “higher-risk” exposures. ¹

Drug choice is influenced by a range of factors including:

- The source’s antiretroviral treatment history.

- Viral load
- Drug resistance (if known)
- The medical history of the exposed person.

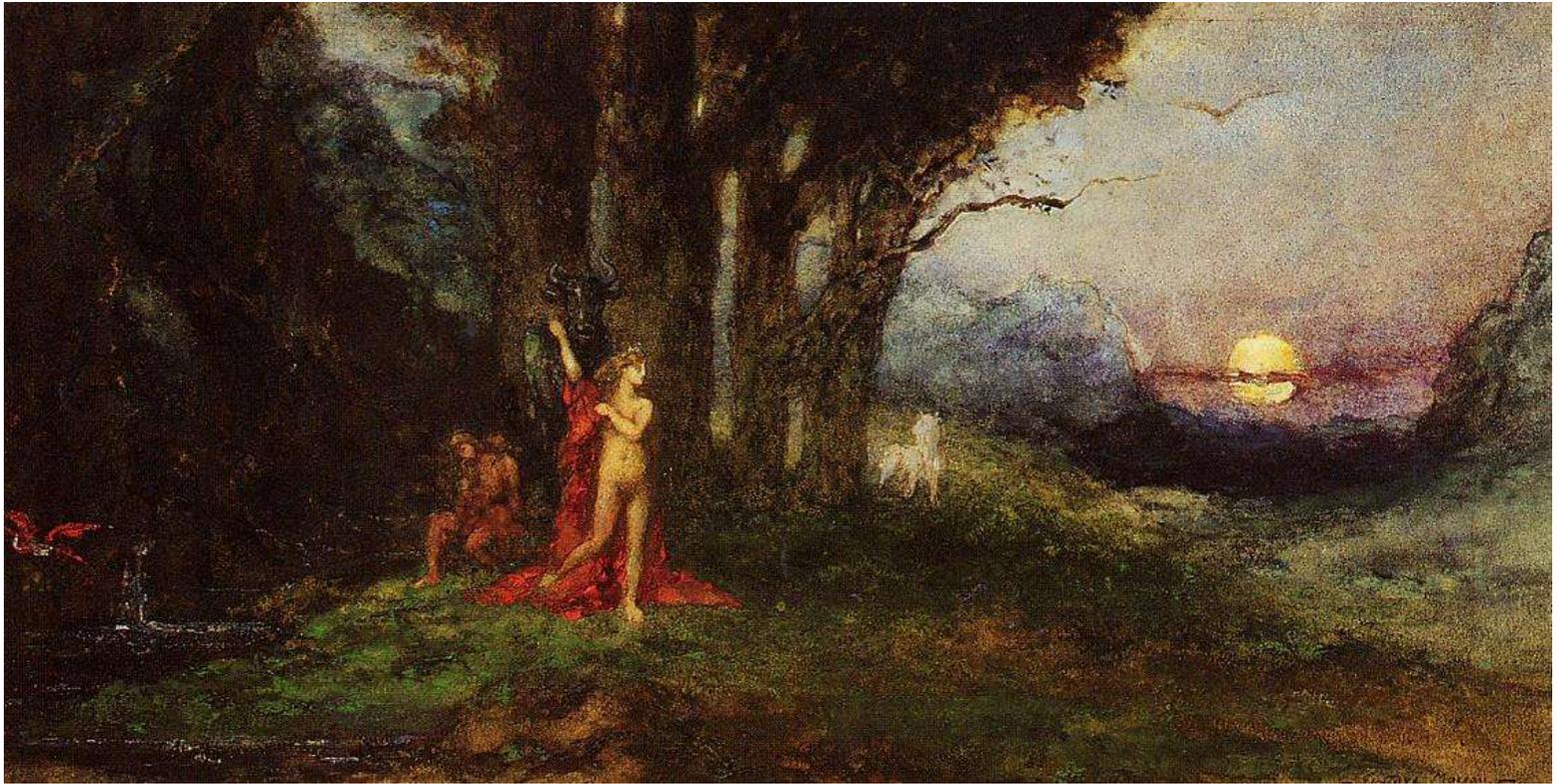
A typical empirical course of treatment is:

- **Truvada 300/200 mg;** one tablet, daily.

In combination with:

- **Raltegravir 400mg;** one tablet, twice a day

Treatment is usually continued for a period of 4 weeks.



"Pasiphae and the Bull", oil on canvas, 1880, Gustav Moreau

References

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