

RALTEGRAVIR



Untitled (Perfect Lovers), 1991, Felix Gonzalez-Torres

*This work, by the Cuban Artist Felix Gonzalez-Torres, so simple at initial glance, seems like it could have been done by a child. And yet it has become an icon of the early dread filled years of the HIV epidemic of the 1980s, a time when a diagnosis of AIDS meant an assured death sentence. But this work could not have been done by a child for many of the reasons that the magisterial Art historian and commentator, Susie Hodge articulated in her book, “Why Your Five Year Old Could **Not** Have Done That”. Felix’s works, have come to be prized by high-end Art connoisseurs, some of his works now selling for millions. This untitled work of 1991, (sometimes referred to as the “Perfect Lovers”) is in fact a superb example of an Art genre that emerged in the late 1960s and early 1970s, that came to be termed “Conceptual Art”. The genre was initially scorned by so-called critics but it quickly captured the interest of the public at large, and became extremely influential, and remains so to the present day.*

Conceptual artists were more concerned with ideas, thoughts, and emotions which they saw as a particular type of “virtual” Art form in their own right. To convey these “memes” that could not readily be put into words and that carried a universal message to all times and to all cultures, they created what the Dadaists would have termed “readymades”, everyday objects displayed or arranged in such a way as to convey an idea, or emotion. But in contrast to the Dadaists who conveyed nonsensical messages simply to convey a spirit of non-conformity and protest, Conceptual Art conveys far more sophisticated ideas. A work of Art is “great” for many different reasons - not simply technical skill and brilliance. Greatness can also include works that are completely original, deeply symbolic, works that become icons of a particular time or a particular place. They can be historical or cultural records that define an age or that helped to change the way in which society thinks. Much of the great Conceptual works of Art make powerful statements about society, culture, politics, and philosophy.

Felix Gonzalez-Torres’s Untitled work of 1991 is Conceptual Art. The two clocks represent two partners. They are simple battery powered devices, initially set at exactly the same time. This represents a conjunction of two lives - mortal lives that both have a limited life span. For a brief moment in time the two are in perfect synchrony. They are also very close to one another. Instructions for a MOMA, New York exhibition included the directions, “When installed, the two clocks must touch... they must be perfectly synchronized including the hour, minute and second hands...they must be displayed on a wall painted light blue.” For Gonzalez-Torres, the color pale blue recalled a beautiful memory. But inevitably two such timepieces will fall out of synch, one moving ahead, or one falling behind, just as two separate lives may do so after the passage of time. Of course at some point one clock will fail, its hands becoming forever frozen in time - a mere fossilized memory of its former vital existence. The metaphorical message of the work relates to inescapable, and inevitable loss of connection with the passage of time. Felix Gonzalez-Torres produced this Conceptual work just after his partner was diagnosed with AIDS in 1991. His partner died shortly after the work was produced.

*Much of Gonzalez-Torres’s work reflected the terrifying atmosphere of the early years of the HIV epidemic, when no effective anti-retroviral agents were available and diagnosis, meant social stigma of the highest order, a lingering morbidity that sat well with the torments of the circles of Dante’s Inferno, and an assured death. Felix’s works made statements about human mortality, relationships and the arrow of time. Many of his simple “readymade” objects were deep meditations of love and loss. His works became iconic symbols of the early years of the HIV epidemic. Untitled (Perfect Lovers), 1991 is one such work, a brilliant work, and a work that could most definitely **not** have been done by a child!*

Felix Gonzalez-Torres died of an AIDS related illness in 1996. In the same year the first highly active anti-retroviral therapy (HAART) agents became available which would revolutionize the treatment of HIV. Since that time newer classes of agents such as the integrase inhibitors continue to emerge so that HIV infection is no longer seen as a death sentence but rather a manageable long term condition.

RALTEGRAVIR

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 protease inhibitor.

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.

Raltegravir is an antiretroviral agent of the integrase inhibitor class.

It is often used together with the fixed-dose combination product **Truvada** for post HIV exposure prophylaxis

This document describes the integrase inhibitor agent **Raltegravir**

History

Raltegravir received approval by the U.S. Food and Drug Administration (FDA) on 12 October 2007.

It was the first of a new class of anti-HIV drugs, the **integrase inhibitors**, to receive such approval

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

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 (or adults):

- 400 mg.

Chewable tablets (for children):

- 25 mg, 100 mg.

Mechanism of Action

Raltegravir targets the HIV enzyme **integrase**, that that is responsible for integrating the HIV viral genetic material into human chromosomes, a critical step in the pathogenesis of HIV.

Inhibition of integrase prevents the covalent insertion, or integration, of the HIV genome into the host cell genome during the early phase of infection.

HIV genomes that fail to integrate cannot direct the production of new infectious viral particles, so inhibiting integration prevents propagation of the viral infection.

Pharmacokinetics

Absorption:

- Raltegravir is administered orally.

It is rapidly absorbed after oral administration.

Distribution:

- Raltegravir is approximately 85 % bound to human plasma proteins.

Metabolism and excretion:

- Raltegravir is eliminated primarily by glucuronidation in the liver (by UGT1A1), and not by CYP enzymes.

Pharmacodynamics

The anti-HIV activity of raltegravir is synergistic with other antiretroviral drugs, in particular, the NRTIs.

Combination therapy also lessens the chance of HIV resistance developing.

Raltegravir is also active against some HIV strains that is resistant to other antiretroviral classes

Indications

Raltegravir is used in *combination* with other antiretroviral drugs (often Truvada) 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

At least 2 other active agents in all patients to minimise development of raltegravir resistance and treatment failure (resistance to raltegravir develops easily if viral replication is not suppressed)

Contraindications/ Precautions

These include:

1. Patients with known hypersensitivity to raltegravir.
2. Drug interactions:
 - **Aluminium and magnesium antacids:**

- ♥ These may reduce raltegravir concentration even when taken 2 hours before or after raltegravir; although the clinical significance of this is currently unknown.

Avoid these combinations and choose calcium carbonate if an antacid is required as it has no significant effect on raltegravir concentration.

- **Rifampicin:**

- ♥ Decreases integrase inhibitor concentration and may reduce its efficacy

Raltegravir is metabolized by glucuronidation (by UGT1A1), not by CYP enzymes. Giving raltegravir with drugs that induce this enzyme (e.g. rifampicin) may decrease its concentration and efficacy.

Conversely, giving raltegravir with drugs that inhibit it may increase its concentration and the risk of adverse effects.

3. Phenylketonurics:

- *Chewable* tablets contain phenylalanine as a component of aspartame.

Pregnancy

Raltegravir is classified as 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

Breastfed infants of HIV-infected mothers are at risk of postnatal transmission; and so breastfeeding should not be undertaken.

Adverse Effects

These include:

1. Non-specific constitutional types reactions:

- Fatigue/ malaise

- Headache
- 2 Liver impairment

Rare but more serious reactions can include:

3. Myopathy/ rhabdomyolysis (elevated CK/ myoglobin levels).
4. Severe dermatological hypersensitivity reactions
 - Stevens-Johnson syndrome/ toxic epidermal necrolysis.
5. Depression:
 - Including suicidal behaviour, particularly with a history of psychiatric illness)

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.



Untitled, billboard of monochrome photograph, 1991, Felix Gonzalez-Torres

One of Felix Gonzalez-Torres' most recognizable "Untitled" works of 1991, were a series of billboards installed in twenty-four locations throughout New York City of a monochrome photograph of an unoccupied bed, made following the death of his long-time partner from AIDS.



Felix Gonzalez-Torres (1957-1996).

References

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Reviewed April 2016.