UNIVERSITAT POLITÈCNICA DE CATALUNYA
BARCELONATECH
Escola Superior d'Agricultura de Barcelona

HIV/AIDS STUDY. BIBLIOGRAPHIC REVIEW OF THE VIRUS AND MATHEMATICAL MODELS.

Bachelor's thesis

Biological Systems Engineering

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18/ June/ 2020

Resum

El virus d'Immunodeficiència humana és una pandèmia global que provoca milers de morts a l'any. És causada per dos lentivirus, poden ser tipus 1 o 2 (VIH-1, HIV-2) i es propaga per sang o fluids corporals. La infecció pel VIH té un període d'incubació de 8 a 10 anys i es caracteritza per atacar a les cèl·lules de CD_4 en el sistema immunitari. Avui en dia, l'organització mundial de la salut (OMS) estima que més de 37 milions de persones viuen amb el VIH a tot el món, de les quals només la meitat tenen accés a la teràpia antiretroviral. La funció principal de la teràpia és reduir la velocitat a la qual el VIH fa còpies de si mateix en el cos mitjançant l'ús de combinacions de fàrmacs.

Avui en dia, el virus del VIH continua tenint un impacte important en el món a causa de la seva ràpida propagació i el nombre significatiu de casos en certes àrees com l'Àfrica subsahariana. Mentre que en la majoria dels països la taxa de creixement tendeix a disminuir, en el cas de l'Àfrica subsahariana, encara està en creixement.

L'ús dels tractaments del VIH i les vacunes han ajudat al no-desenvolupament del virus, però, el problema es manté. És per això que s'han utilitzat altres eines en els últims anys per prevenir i analitzar el problema de l'epidèmia, com ara l'ús de models matemàtics. Aquests ens poden fer entendre l'evolució del VIH al món com també el curs clínic del VIH.

En aquest treball es planteja una revisió bibliogràfica del coneixement actual sobre el VIH, així com dels models matemàtics que s'han utilitzat en el seu estudi. Aquest treball és el punt de partida d'una nova línia de recerca del Grup de Biologia Computacional i Sistemes Complexos de la Universitat Politècnica de Catalunya.

Resumen

El virus de la inmunodeficiencia humana es una pandemia a nivel mundial que causa miles de muertes al año. Esta causada por dos lentivirus, ya pueden ser del tipo 1 o 2 (VIH-1, VIH-2) y se contagia mediante la sangre o fluidos corporales. La infección por VIH tiene un periodo de incubación de 8 a 10 años y se caracteriza por atacar a las células CD_4 del sistema inmunitario. Hoy en día, la Organización Mundial de la Salud (OMS) calcula que más de 37 millones de personas viven con el VIH en todo el mundo. De los cuales, solo la mitad tiene acceso a la terapia antirretroviral. La función principal de la terapia es reducir la velocidad a la que el VIH hace copias de sí mismo en el organismo mediante el uso de combinaciones de medicamentos.

Hoy en día, el virus del VIH sigue teniendo una gran repercusión en el mundo debido a su rápida propagación y a la notable cantidad de casos en ciertas zonas como es el caso del África Subsahariana. Mientras en la mayoría de los países el índice de crecimiento tiende a bajar, en el caso de África subsahariana sigue en crecimiento.

El uso de tratamientos y vacunas para el VIH han ayudado al no desarrollo del virus, aun así, el problema sigue vigente. Es por ello, que en los últimos años se han usado otras herramientas para prevenir y analizar el problema de la epidemia, como es el caso del uso de modelos matemáticos. Estos, nos pueden hacer entender la evolución del VIH en el mundo como es también el curso clínico del VIH.

En este trabajo se plantea una revisión bibliográfica del conocimiento actual sobre el VIH, así como de los modelos matemáticos que se han utilizado en su estudio. Este trabajo es el punto de partida de una nueva línea de investigación del Grupo de Biología Computacional i Sistemas Complejos de la Universidad Politécnica de Cataluña.

Abstract

The human immunodeficiency virus is a global pandemic that causes thousands of deaths a year. It is caused by two lentivirus that can already either type 1 or 2 (HIV-1, HIV-2) and are spread by blood or bodily fluids. HIV infection has an incubation period of 8 to 10 years and is characterized by attacking CD_4 cells in the immune system. Today, the World Health Organization (WHO) estimates that more than 37 million people live with HIV worldwide, of which only half have access to antiretroviral therapy. The main function of the therapy is to reduce the rate at which HIV replicates in the body by using combinations of drugs.

Nowadays, the HIV virus continues to have a major impact on the world due to its rapid spread and the significant number of cases in certain areas, specifically sub-Saharan Africa. While in most countries the growth rate tends to fall, in the case of sub-Saharan Africa it is still growing.

The use of HIV treatments and vaccines have helped in the non-development of the virus, yet the problem still remains. That is why other tools have been used in recent years to prevent and analyze the problem of the epidemic, such as the use of mathematical models. These can help us understand the evolution of HIV in the world as is the HIV clinical course.

In this work, a bibliographic review of the current knowledge about HIV is proposed, as well as the mathematical models that have been used in its study. This work is the starting point of a new line of research of the Computational Biology and Complex Systems Group of the Polytechnical University of Catalonia.

Summary

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1 Introduction

1.1 Human Immunodeficiency Virus (HIV)

The human immunodeficiency virus (HIV) is one of the most significant diseases of global concern, affecting all regions of the world and causing millions of deaths and new infections every year. HIV is characterized by attacking individuals' immune systems, which causes the body to fail in fighting certain diseases. The human immunodeficiency virus is determined by three different phases. The first is acute infection, the second is chronic infection and finally we have AIDS (Acquired Immune Deficiency Syndrome), being the most serious of phases. A person has advanced to AIDS disease when their CD_4 cell count is less than 200 cells/mm^3.

HIV is transmitted through different bodily fluids, although the most common way to spread is through unprotected sexual intercourse with an infected person. HIV can also be transmitted during the pregnancy, although this is less common.

People who get the infection feel healthy for a long time. It may take ten or more years for the first symptoms to develop (Kirchhoff *et al.*, 1995). In the first month of becoming infected, people may feel fever, pain, and discomfort in the body, but these symptoms are similar to those of the flu and are often confused.

HIV is a syndrome that nowadays has no cure, but there are several methods that help us prevent the virus. These include pre-exposure prophylaxis and post-exposure prophylaxis. Pre-exposure prophylaxis helps us prevent HIV transmission in people at high risk of infection. On the other hand, post-exposure prophylaxis is used after possible exposure to HIV to reduce the chances of getting the infection. Antiretroviral treatments may also be performed to prevent the virus from reproducing. This is done by reducing its viral load, thus preventing the deterioration of the immune system. The sooner you start antiretroviral treatment, the more likely you are to recover. Currently, there are many medicines for the treatment of HIV, but the selection of these drugs depends on several factors, such as possible adverse effects and drug interactions.

1.2 Mathematical models of HIV

Another part of the work to be discussed are the mathematical models that exist and their different applications to apply to the current HIV situation. A mathematical model is a process that allows us

to understand the internal processes and the relationships between them through a system of equations.

The classification of the models is varied and depends on their study purpose. In epidemiology, two types of mathematical models are typically used. IBM models, have a very high stochasticity but also, they can be deterministic. In addition, they are characterized by a bottom-up approach. On the other hand, compartmental models, which have a very high deterministic character with some stochastic parts, are characterized by a top-down approach. Hybrid models that mix the previous two types of models can also be found.

To model an epidemic, it is common to build models in compartments to describe its dynamics. In these models, the population is divided into three classes - the susceptible, the infected and the recovered (SIR). Although we can also find other types of mathematical models such as SEIR (susceptible, exposed, infected, recovered).

Mathematical models are also useful in order to understand the natural history of the diseases, allowing us to understand its conduct within a host and which factors favor or hinder its development.

In this study, different articles have been reviewed in order to understand how the virus works. Different mathematical models have been described in this work through tables, distributing them according to whether they are epidemiological models or models of natural history. In them you can find information related to the elements considered, whether the process incorporates treatment, and the equations given by the article.

The final part of the work will include the implementation of different mathematical models using the Matlab program in order to be able to understand the evolution of the virus.

1.3 Current context

This project is developed with the Computational biology and complex systems team (BIOCOM-SC). It is a research group dedicated to working with infectious diseases, which mostly affect people with fewer resources such as tuberculosis, Chagas disease or malaria.

BIOCOM-SC aims to study HIV and AIDS in the near future, which is why the work carried out focuses on the bibliographic part of the infection dynamics, as well as on existing mathematical models, in order to help the team commence their study.

1.4 Objectives

This bachelor thesis represents the beginning of a new line of research that aims to study the behavior of the virus, as well as its properties.

In this work, the study of the human immunodeficiency virus (HIV) is conducted in order to see how it affects humans, thus facilitating the understanding of its functioning.

General objectives:

To study the properties and epidemiology of the human immunodeficiency virus and to carry out the development of a mathematical model.

Specific objectives:

1. Conduct a literary review of human immunodeficiency virus.
2. Study the epidemiology of the virus.
3. Conduct a literary review of mathematical models in HIV epidemiology.
4. Develop a mathematical model, as simple as possible, to understand the behavior of the cells within the infected organism.

Outline:

This bachelor thesis is divided in 5 chapters. The first chapter is the introduction where a general idea of the work done is described.

In the second chapter a literary review on HIV is presented, including all important information on the virus and its epidemiology.

The third chapter presents the models and its implementation on Matlab. On the one hand, a basic viral dynamics model is illustrated and explained in order to understand the behavior of the virus without taking antiretroviral therapy. On the other hand, a model under antiretroviral therapy is shown with the aim of comparing the evolution of the virus with or without treatment.

Finally, the fourth and the fifth chapters describe the conclusions and the prospects of the bachelor thesis, respectively.

2 HIV bibliographic review

2.1 Human Acquired Immunodeficiency Virus (HIV)

HIV is a virus that spreads through certain bodily fluids and attacks the body's immune system, especially CD_4 cells, also known as T cells (Figure 2.1-1). CD_4 cells are responsible for helping the immune system fight infections. Therefore, an HIV infection can cause difficulty in the body to fight certain infections and some types of cancer. The most advanced stage of HIV infection is known as AIDS. A person with HIV is considered to have progressed to AIDS when:

- The number of CD_4 cells is less than 200 cells/mm^3. Normally, people with a healthy immune system the number of CD_4 cells is between 500 cells/mm^3 and 1600 cells/mm^3.
- They develop one or more opportunistic infections regardless of CD_4 cell count.

Once infected with HIV, the virus remains perpetually in your body. There is no cure, but there are medicines that can help you feel better and not spread to others. Without taking medication, people with AIDS usually survive about 3 years. However, people who start antiretroviral processing shortly after getting HIV experience more benefits (*What Are HIV and AIDS? | HIV.gov*).

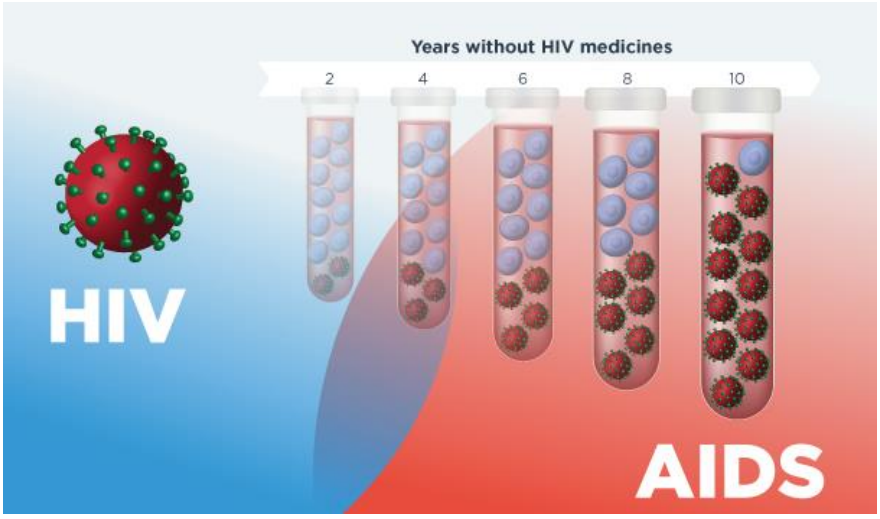


Figure 2.1-1 Evolution from HIV to AIDS. In blue we have represented CD_4 cells while in red we have the HIV virus as the years progress without taking drugs (*VIH/SIDA: Conceptos básicos | El VIH/SIDA | infoSIDA*).

As mentioned before HIV is caused by the two lentiviruses, HIV-1 and HIV-2. Both viruses are the result of multiple transmissions of simian immunodeficiency virus (SIV) that naturally infect African primates. For this reason, it is believed that AIDS originated in Africa and that the disease reached humans through wild chimpanzees and sooty mangabeys.

Although the origin of AIDS is still unknown today, the most accepted theory states that it was contracted from people who hunted and ate infected chimpanzees. Researchers place the origin of the virus in humans around 1930 based on scientific calculations on the time it takes for different HIV strains to evolve *(Sharp,P., Hahn,B. 2011).*

At the end of 1970, sporadic cases of a rare disease began to be detected, all of them with a common denominator: candida albicans infection in the mouth and esophagus, accompanied by rashes in different parts of the body. These rashes corresponded to an aggressive form of Kaposi sarcoma, pneumocystis carinii pneumonia, and in some cases, neurological damage and unexplained immune system suppression.

On June 5, 1981, Gottieb, Siegal and Masur published the first reports of different cases of young homosexuals having pneumonia for Pneumocystis carinii. The immune system of these young people was weakened and almost disappeared, and there was no relationship between them. Finally, they associated these manifestations with a decrease in T4 lymphocytes, as well as the possible onset of Kaposi sarcoma (*Analisis Consumo Drogas | Farmaceuticos | Historia Del Vih/Sida|*).

On 24 September 1982, the criteria, diagnosis and definition of the new condition were established by the Center for Disease Control. In addition, the FDA proposed to designate the newly acquired immunodeficiency syndrome disease *(Gómez,M., Nápoles, M. (2009)).*

2.1.1 Retrovirus properties

HIV is a virus in the family Retroviridae. Within it, is located in the subfamily lentivirinae. Retroviruses are viral agents that are characterized by having an enzyme called reverse transcriptase, capable of transforming RNA into DNA.

Two different types of lentivirus *(Rosas, 2013)*, HIV-1 and HIV-2 have been identified. Although they have many common antigens, from a serological point of view and geographical distribution, they

are somewhat different. Phylogenetically, HIV-2 and VIS have a 75% similarity in their nucleotide sequence, while HIV-1 and HIV-2 have a similarity of 60%.

Both lentiviruses are spherical, 90-130nm in diameter, and contain a cone-shaped electrodense nucleocapsid. This nucleocapsid is surrounded by a lipid bilayer that comes from the membrane of the host cell. Within this host cell we find 80 spicules, each consisting of several gp120 molecules being inserted non-covalently to an integral membrane protein, gp41. These two viral glycoproteins are essential for the virus to infect cells. The nucleus of the virus contains: the capsid protein, p24 in HIV-1 and p26 in HIV-2; nucleocapsid p7/p9 protein, two copies of RNA; and three viral enzymes (protease, reverse transcriptase, and integrase).

One feature that distinguishes the two lentiviruses from other retroviruses is the complexity of their genome. The HIV genome consists of two single-chain RNA molecules of 9400 base pairs, joined by non-covalent bonds. The classic structural genes gag, pol, and env encode precursor proteins that will then be divided by protease into mature proteins. In addition, the genome also has other genes: tat, rev, vif, nef, vpr and vpu, responsible for regulating the synthesis and organization of infectious viral particles. In addition, in the provirus state, the genome is flanked by long repeated sequences (LTRs) involved in the integration of the viral genome into the host cell genome, containing the elements of viral transcription and polyadenylation.

2.1.2 HIV life cycle

Because HIV has no self-replication capability, as it lacks DNA and other auxiliary organelles to perform this process, it needs to invade a host cell. The infection starts when a complete viral particle encounters a cell with CD_4 receptor. Glycoprotein gp120 is then attached to this receptor. To mediate the fusion of the virus to the cell, receptors are needed for chemokines because for the cell to be infected with HIV, it must also express a coreceptor to which the gp41 will bind.

There are two types of coreceptors, present in different types of cells:

- CXCR-4: found in T cells.
- CCR-5: found in monocytes and macrophages.

The HIV biological cycle is divided into two different stages (Figure 2.1-2). The first stage ranges from cell recognition to the integration of viral DNA into host DNA. Cell recognition is performed by CD_4 receptors in a T_4 lymphocyte. The virus wrapping is composed of two glycoproteins (gp120 and gp41). The gp120 performs the process of coupling when it binds to the target cell receptors. This

binding causes a conformal change in gp120, which allows it to fold to gp41 and insert its non-polar terminals to the cell membrane. This allows the fusion of the viral envelope of gp41 with the cell membrane, accessing the ingress and fragmentation of the nucleocapsid giving way to the release of virogenetic-enzymatic components. Once the RNA is released into the cell cytoplasm, the reverse transcriptase begins the retrotranscription process. This process is initiated at the active site of polymerase, which transforms viral RNA into a complementary DNA chain, giving rise to a double RNA-DNA helix. Subsequently, the ribonuclease site separates the double RNA-DNA chain by eliminating the simple RNA chain. Again, the polymerase site synthesizes a consensus sequence to the simple sequence of backtranscribed nucleotides, forming a useful string of viral DNA. The integrase then creates cohesive ends in the viral DNA chain so that it can be integrated into the host cell genomeending the first half of its biological cycle.

The second stage of the HIV biological cycle ranges from the biosynthesis of the viral components to the output of the virions. Initiation of provirus transcription depends on cellular and viral factors that interact with regulatory sequences located in the U3 region of the LTR. These cellular elements bind to the viral promoter and increase the genetic expression of HIV-1 in response to cell stimulation by different mechanisms. An example of these would be exogenous cytokines, which along with cell stimulation, allow the formation and activation of the primary transcriptional complex with cellular polymerase II RNA. The generated RNA is processed in the nucleus and transported to the cytoplasm with the help of the viral protein Rev, where it is translated by giving the different viral proteins, which travel to the assembly centers to form the new virions, which are released through a moaning process through the plasma membrane. A key enzyme in the formation of virions is viral protease, an enzyme that causes the breakdown of Gag polyprotein in capsid and nucleocapsid proteins (p6, p9, p17, p24) and Polyprotein Pol, precursor of all viral enzymes of HIV-1 (protease, integrase and reverse transcriptase). The final maturation of the virions and the correct assembly of the viral proteins occurs at the end of the infective cycle. The nucleocapsid leaves the cell taking with it a membrane fragment ending the assembly process and the output of the virion.

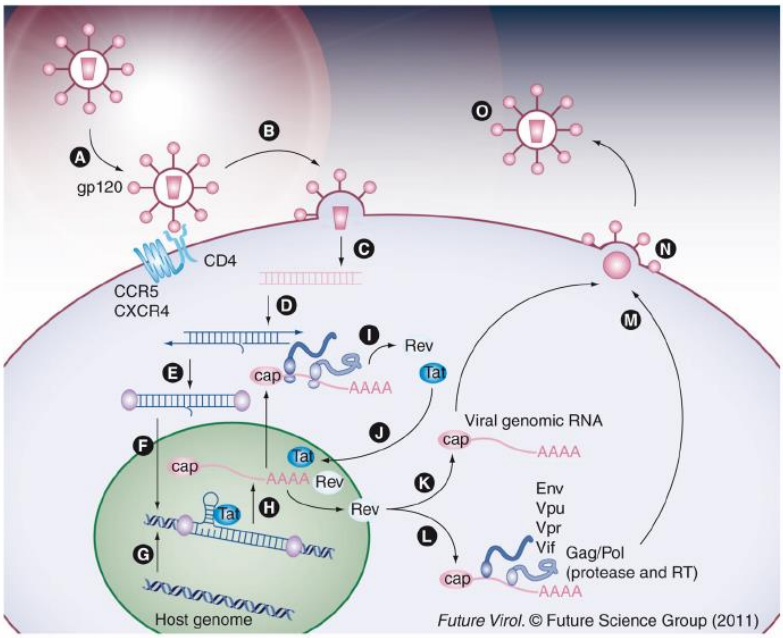


Figure 2.1-2 The HIV-1 life cycle. DNA is shown in blue while RNA is shown in pink. (A)Adsorption (B) Fusion (C) Uncoating (D) Reverse transcription (E)Formation of the pre-integration complex (F) Nuclear import of pre-integration complex (G) Integration of viral cDNA into host genome (H) Transcription of the proviral DNA (I) Translation of Tat and Rev (J) Import of Tat and Rev into the nucleus (K) Rev facilitates the export of full-length HIV-1 RNA genome for packaging (L) Rev exports unspliced and singly spliced HIV-1 transcripts to the cytoplasm (M) Assembly (N) Budding (O) Maduration *(Chung, Rossi and Jung, 2011)*.

2.1.3 Clinical manifestations

HIV infection is characterized by a wide variety of clinical phases with their respective manifestations. These include acute retroviral infection or acute retrovirosis, as well as the following phases: asymptomatic HIV infection and finally AIDS (Figure 2.1-3) (*The Stages of HIV Infection AIDSinfo*).

a. Acute retroviral infection

This phase corresponds to the arrival of the virus to the patient. In most cases, it is usually asymptomatic, but there is the possibility that it may become symptomatic, where the clinical picture presents varied symptoms. Here we can highlight general symptoms (fever, pharyngitis, lymphadenopathies box similar to that of infectious mononucleosis, arthralgias, myalgias, anorexia and weight loss); dermatological (maculopapular erythematous rash, diffuse hives and alopecia), gastrointestinal (nausea, vomiting, diarrhea and mucocutaneous) and neurological ulcerations

(headache, retroorbitarian pain, meningoencephalitis, peripheral neuropathy, radiculitis and Guillain-Barré syndrome) *(Lamotte, J.A. (2014))*.

Doctors and patients often do not care because they are very nonspecific symptoms, so it is difficult to determine exactly if they are signs of HIV. Generally, these symptoms have a period of approximately 6 to 8 weeks and do not require specific treatment *(Antonio and Castillo, 2004)*. During this phase there is the disadvantage that HIV serology is negative, although viral antigens are positive.

b. Chronic infection

The second stage of HIV infection is chronic HIV infection, also known as a clinical or asymptomatic latency period (*The Stages of HIV Infection | Understanding HIV/AIDS | AIDSinfo*). During this phase, the virus continues to multiply at very low levels, which is why people with chronic infection do not have any HIV-related symptoms. Without antiretroviral drugs (ART) the infection progresses to AIDS in 10 years or more, although in some people it may move faster. Those who take ART may be in the asymptomatic phase for several decades. Chronic phase is usually asymptomatic, although symptoms of adenic syndrome may also occur.

c. AIDS

AIDS is the final and most serious phase of HIV infection. Because the virus has destroyed the immune system, the body cannot fight opportunistic infections (*¿Qué Es Una Infección Oportunista? | El VIH/SIDA | Infosida (2019*) or cancer. From an immunological point of view, it represents severe immunosuppression, with a noticeable depletion of the number of CD_4 lymphocytes. People with HIV are diagnosed with AIDS if they have a CD_4 lymphocyte count of less than 200/mm^3 or if they have certain opportunistic infections. Once the person receives AIDS diagnosis, they can have a very high viral load and transmit HIV to others very easily. As mentioned before, without treatment, people with AIDS usually survive about 3 years.

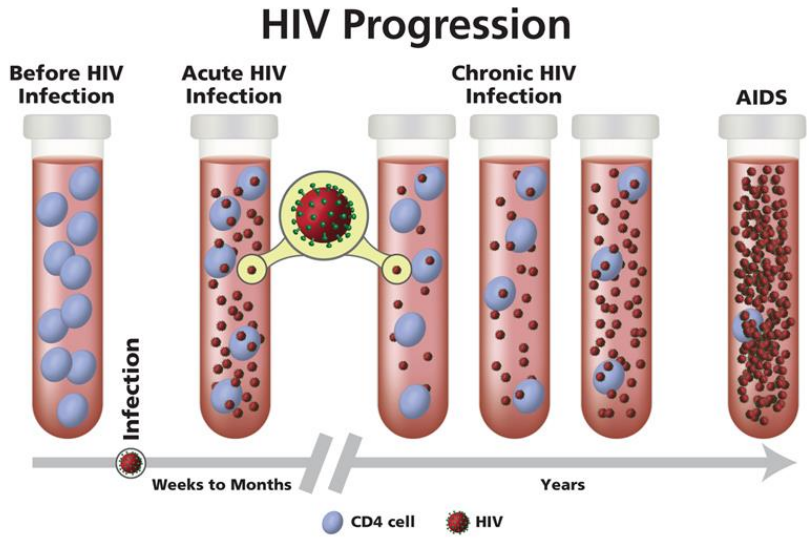


Figure 2.1-3 HIV progression. Distributed in three phases: Acute HIV infection, Chronic HIV infection and AIDS. In blue are represented the CD_4 cells, on the other hand, in red are represented the virus.
(*HIV Progression | Definition | AIDSinfo*)

2.1.4 HIV transmission

The most common ways to transmit HIV occur through sexual intercourse, whether or vaginal with a person who has the disease without using condoms, or through the use of contaminated needles or syringes (Table 2.1-1) (*Transmisión del VIH | Información básica | VIH/SIDA | CDC*). HIV can survive on a used needle for 42 days, but it also depends on environmental factors. Less commonly, HIV can be transmitted through pregnancy, childbirth or breastfeeding. The risk may be high if the mother has HIV and is not taking medication. The following are high-risk groups for acquiring the infection *(Cordeiro and Taroco, no date)*:

- Gay or bisexual males, currently transmission in this group is in regression.
- Intravenous drug users.
- Non-intravenous (inhalation) drug users.
- Hemophiliacs.
- Blood receptors and non-hemophilic blood cells.
- Heterosexual contacts of members of other risk groups (making up 10% of the sick).

Finally, there are extremely rare cases of HIV transmission (*Transmisión del VIH | Información básica | VIH/SIDA | CDC*) such as:

- Oral sex. In general, the risk of getting HIV through oral sex is very low.

- Blood transfusions, tissue transplants, or organs that are contaminated by HIV due to the rigorous analysis of donated blood, organs and tissues.
- Eating food that was bitten by a person infected with the virus. Contamination occurs when blood in the infected person's mouth is mixed with food.
- The bite of a person with HIV. There is no risk of transmission if the skin does not break.
- Contact between HIV-infected blood or body fluids with infected blood and open skin, wounds, or mucous membranes.
- Deep kisses if both people have bleeding sores or gums.

Table 2.1-1 Estimated risk of contagion as a percentage, depending on the type of exposure occurring (*Probabilidades de contraer el VIH | Consultorio TodoSida ¡Acción de prevención contra el VIH/SIDA/ITS!*).

Exposure time	Estimated risk of infection
Transfusion a unit of blood	90-100%
Percutaneous (blood)	0.3%
Mucocutaneous (blood)	0.09%
Receptive anal intercourse	1-2%
Active anal intercourse	0.06%
Vaginal intercourse (female)	0.1-0.2%
Vaginal intercourse (male)	0.03-0.14%
Oral sex to man	0.06%
Urogenital woman- woman	Only 4 registered cases
Sharing injection material	0.67%

The main form of infection in the world is through sexual transmission, this comprises 75% of all cases (Cordeiro and Taroco, no date). The propagation rate for this method is higher than any of the others. The virus travels in semen, free and inside the lymphocytes, vaginal secretions, and cervical mucosa cells of infected women. It is considered that the risk of transmitting HIV from man

to woman during sexual intercourse carries twice the risk than transmitting the virus from woman to man. Infection from woman to male depends on the type of virus and its virulence.

HIV can be transmitted in two ways:

- Using Langerhans cells (dendritic cells) of the mucosa
- By direct inoculation in blood vessels broken by trauma, due to sex.

Mother-child transmission is the most common cause of pediatric AIDS. There are three transmission pathways:

- Inside the uterus, through transplacental propagation.
- During childbirth, through the infected canal of birth.
- After birth, by ingestion of breast milk.

The risk of this transmission can be reduced with HIV serological studies during pregnancy controls and with timely treatment. Between 10% and 35% of children born to infected untreated mothers develop the infection. The same infection can occur intra-utero followed by the development of AIDS and death in the first years. If the infection is perinatal, the installation of AIDS is delayed.

2.1.5 Transmission difference in men and women

According to the article *(Ziegler and Altfeld, 2016)*, there are sexual differences in various infectious and autoimmune diseases. During HIV-1 infections, women have been shown to have lower levels of viral plasma load in primary infection *(Meditz, A., Mawhinney, S., et al. (2011))*. However, in chronic infections, women with the same viral load have a 1.6 times higher risk of developing AIDS. In addition, women infected with HIV-1 tend to have higher levels of immune activation and gene expression for the same viral load.

The mechanisms responsible for these reported sex differences in viral load and CD_4^+ T cell counts remain unknown. However, the role of sex hormones has been postulated (Farzadegan *et al.*, 1998). It is important to understand the biological factors underlying these gender differences, as women are overly affected by HIV-1, in particular, young women in sub-Saharan Africa. HIV-1 infection is now one of the leading causes of death in women of reproductive age, and according to the WHO, AIDS has become the leading cause of death in adolescent women.

2.1.6 HIV symptoms

a. First symptoms

Initially people who get HIV feel healthy for a long time. As mentioned, it may take 10 years or more for the HIV infection to develop symptoms, and even longer for individuals taking antiretrovirals. That is why regular HIV testing is critical. Especially if you have had unprotected sex or shared needles. Treatment may decrease your chances of spreading it to others.

The first 2 to 4 weeks after getting HIV, you may feel a little fever, pain, and discomfort. The symptoms are similar to those of the flu and it is the body's first reaction to infection (table 2.1-2). During this stage there is a high concentration of the virus in the body, so it is easy to transmit it to other people. Symptoms go away after a few weeks and do not recur until many years have passed.

Table 2.1-2 First symptoms to detect if a person has contracted HIV (*¿Cuáles son los síntomas del VIH/SIDA?*).

Sores	Headache	Blood from the mouth, nose, anus, or vagina	Neck pain
Weight loss	Skin rashes	Fungal infections	Bruising formation
Numbness of the hands or feet	Chronic inflammatory pelvic disease	Diarrhea, fever, or night sweats	Loss of control over muscles and reflexes
Serious infections	Inflamed glands	Inability to move	Persistent tiredness
Dry and deep cough	Loss of muscle strength	Dizziness and stuns	Feeling short of breath

b. Late symptoms of infection

HIV destroys immune system cells, known as CD_4 cells or T cells. Without CD_4 cells, the body finds it difficult to fight diseases. Over time, the damage that HIV causes to the immune system results in AIDS.

A person is considered to have AIDS when they suffer from rare infections (Table 2.1-3), certain foreign cancers, or have an extremely low CD_4 cell count *(Cordeiro and Taroco, no date)*.

Table 2.1-3 AIDS indicator diseases *(Cordeiro and Taroco, no date)*.

Opportunistic infections	
Protozoa	Cerebral toxoplasmosis Cryptosporidiosis with diarrhea Isosporidiasis with diarrhea
Fungi	Esophageal, tracheal, and pulmonary candidiasis Pneumonia by *Pneumocystis carinii* Extrapulmonary cryptococcosis Disseminated Histoplasmosis Disseminated coccidioidomycosis
Virus	Cytomegalovirus disease Persistent or spread infection with Herpes Simplex virus Progressive multifocal leukoencephalopathy
Bacteria	Infection spread by members of the *Mycobacterium avium* complex Atypical mycobacteria infections Extrapulmonary tuberculosis Recurrent septicemia by *Salmonella sp*. Multiple or recurrent infections from pyogenic bacteria
Opportunistic Neoplasms	
Kaposi's sarcoma Primary brain lymphoma Other non-Hodgkin's lymphomas	
Other	
HIV cachexia syndrome HIV encephalopathy Lymphoid interstitial pneumonia	

2.1.7 Diagnosis

HIV detection can be done through direct and indirect testing (*Pruebas de detección del VIH | El VIH/SIDA | infoSIDA*).

a. Direct testing

These tests consist of an early diagnosis of HIV infection by detecting the existence of the virus or its components (proteins and nucleic acid) even before antibodies create an immune response to it. Some of the tests used are p24 antigenemia, viral culture and polymerase chain reaction.

b. Indirect testing

There are three types of indirect tests to diagnose HIV infection. These tests can only detect the infection based on the person's silent period. The silent period is the time between the time of a person's possible exposure to HIV and when a test allows accurate detection of HIV infection (Figure 2.1-4). These tests detect the immune response of CD_4 cells in the infected person's body. Serological tests to diagnose HIV detect antibodies to HIV-1 and HIV-2 in addition to the p24 antigen of the virus. It should be noted that serological tests locate the antibodies that the body generates as an immune response, and not the virus.

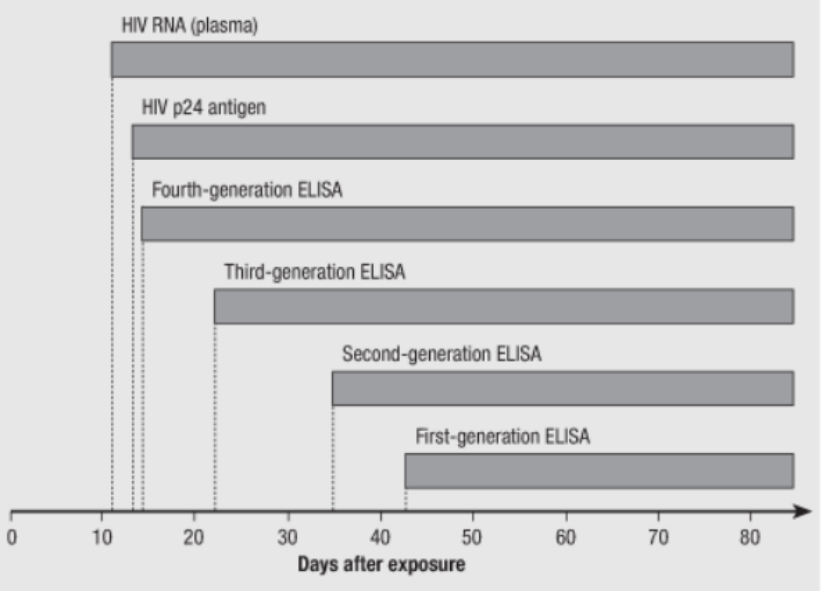


Figure 2.1-4 Time of detection of specific markers for HIV infection based on exposure days. Time 0 indicates time of HIV infection (Buttò *et al.*, 2010).

- Screening tests

The most commonly used detection tests are ELISA serology and rapid testing, although there are also others such as p24 antigenemia and chemoluminescence used to a lesser extent (Álvarez, R.I. (2017)).

The ELISA (Enzyme-Linked Immunoabsorption Assay) method also called enzymoimmunoanalysis (EIA), is a test that detects both the p24 antigen of the virus and antibodies against HIV-1 and HIV-2 within 13-15 days of being exposed to infection, there are four different types of serologies, the most commonly used are the fourth generation (Figure 2.1-5), allowing diagnosis in 80-90% of cases of the first-generation phase. The first techniques were developed in 1985, used a viral lysing as an antigenic basis, and antibodies were detected 40 days after infection *(García et al., 2011)*.

If the screening test is positive a confirmation test is required, the most used method is the Western Blot (WB)

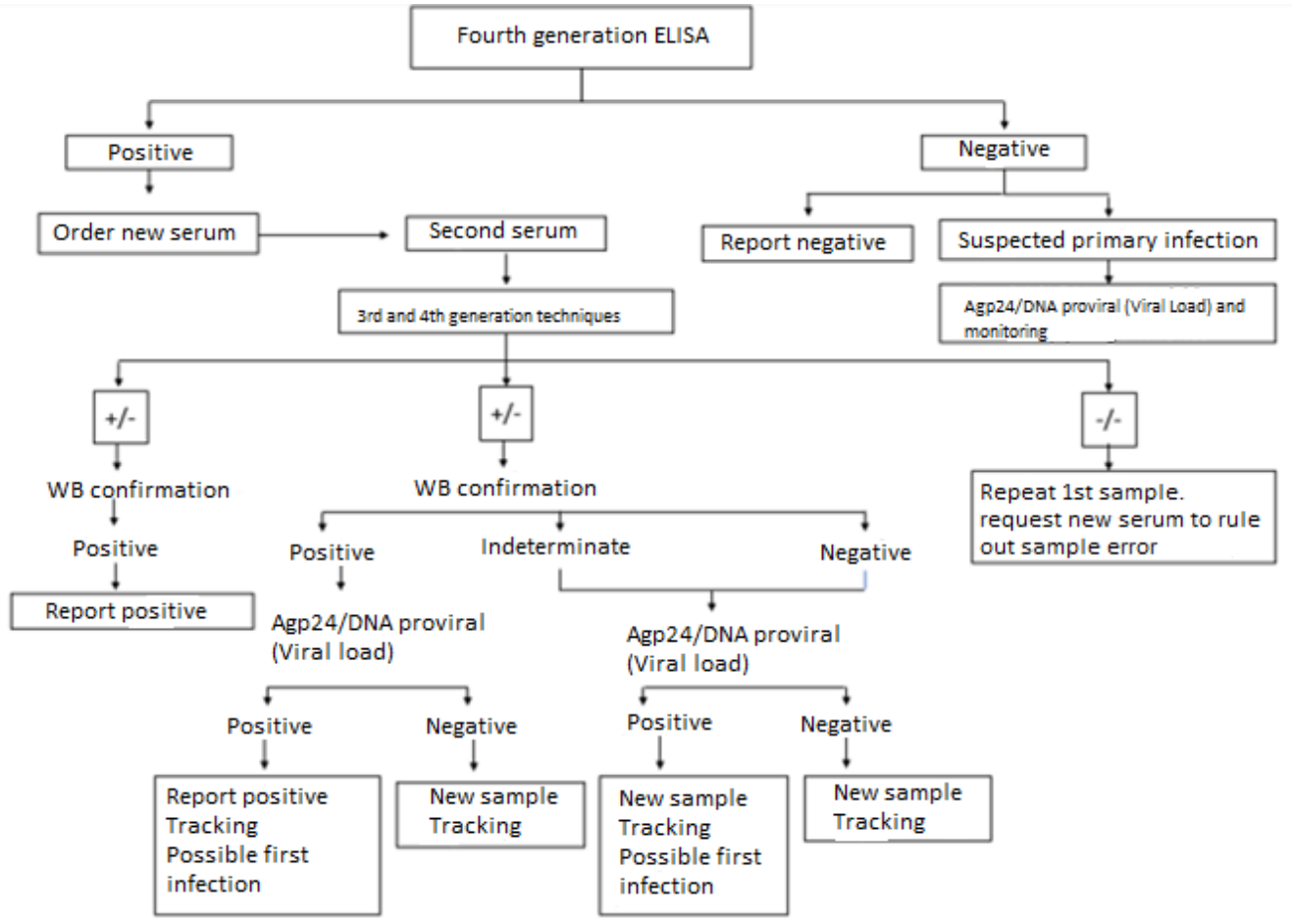


Figure 2.1-5 Diagram of the screening test procedure, fourth generation ELISA serology *(García et al., 2011)*.

- Quick tests

The distinguishing feature of these tests (Figure 2.1-6) is that their run time is about 20 minutes. In addition, you do not need special equipment and have built-in internal quality control systems. In general, they have a sensitivity comparable to ELISA tests, but their specificity is usually less.

If the result is positive, confirmatory tests are required, immunochromatography is the most used method, although there are also other methods such as agglutination, immunoconcentration and solid phase.

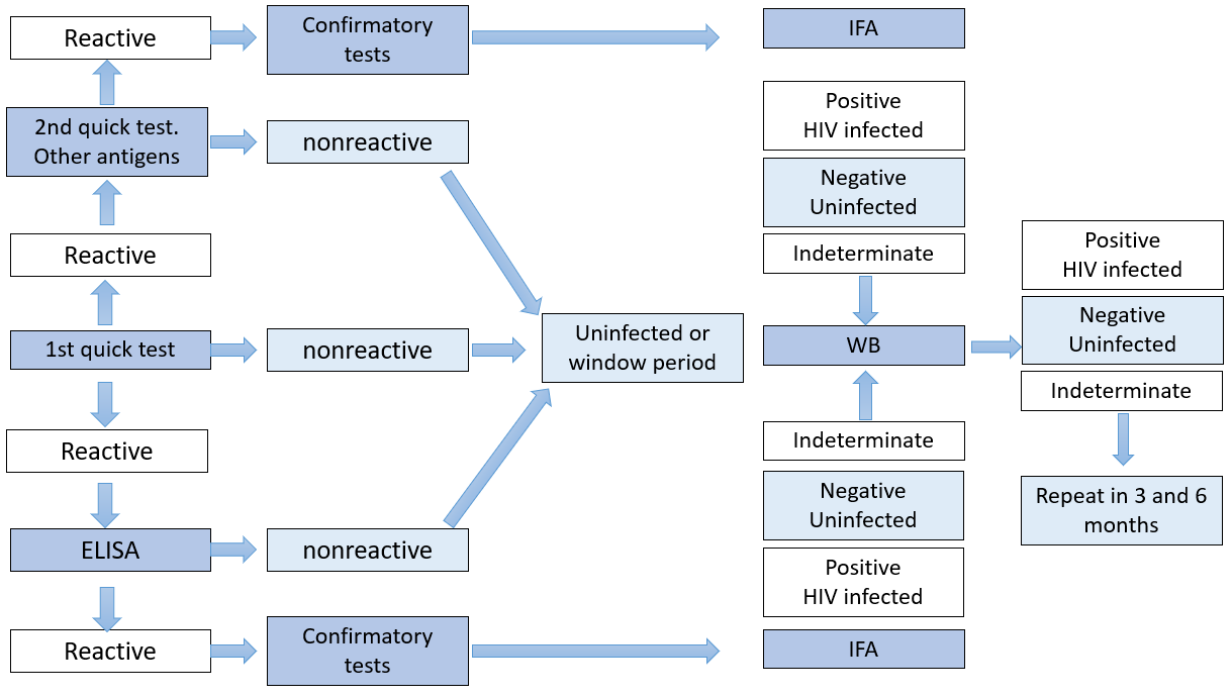


Figure 2.1-6 Quick testing procedure. Starting at 1st quick test *(Álvarez, R.I. (2017))*.

- Confirmatory evidence

The most commonly used confirmatory techniques are Western Blot (WB) and recombinant immunoblot or online immunoassay (LIA) that have at least the same sensitivity as ELISA and superior specificity *(García et al., 2011)*.

Western Blot is a methodology in which the different viral proteins are separated according to their molecular weight by electrophoresis in the polyacrylamide gel and transferred to a nitrocellulose membrane on which the patient's serum is added and incubated. If the serum has antibodies to a protein, a colored band is produced that defines the reactivity of WB. It detects antibodies to the wrapping glycoproteins gp160, gp120 and gp41, those encoded by the gag gene p55, p24 and p17 and the enzymatic proteins p66, p51 and p31.

A person is only considered to be HIV-infected when the confirmatory test result is positive. An indeterminate result could result from HIV-2 infection, seroconversion, advanced stage of HIV infection or children of HIV-positive mothers. In this case, a second sample should be analyzed by EIA and WB at 3-6 months along with other complementary tests (PCR).

Other confirmatory tests include immunoelectrotransfer analysis, immunofluorescence analysis, and radioimmunoprecipitation analysis, although due to their complexity and high subjectivity they are not commonly used for confirmatory tests.

- Supplemental and immunological tests

This type of testing aids in the diagnosis of HIV infection, checks how the infection evolves, and informs of the degree of immunosuppression.

  - Detection of antigenemia

Detection of specific antibodies indicates exposure to the virus and infection. Direct detection of the viral antigen p24 introduces a dynamic characteristic in serology since, being a viral replication index, it provides information about the current state of infection. This viral antigen is detected in early stages of infection, or during the evolution to AIDS, and supports serological diagnosis in situations where antibody detection is inconclusive.

  - Determination of proviral DNA

Proviral DNA corresponds to the viral genome embedded in the cell genome which the virus infects. It can be used to assess mother-child transmission in the diagnosis of vertical HIV transmission and for monitoring post-exposure prophylaxis

  - Determination of plasma viremia (viral load)

Plasma viremia, also known as HIV viral load, is defined as the number of RNA copies of the virus found in plasma. Its determination, together with the CD_4 lymphocyte figure and the clinical situation of the patient, is used to establish therapeutic decisions, as well as for the monitoring of antiretroviral therapy. It is one of the factors to be assessed to decide whether treatment should be initiated, although the main indicator in these cases is CD_4 lymphocyte count.

Table 2.1-4 Initiation of Truvada treatment for use of PrEP in different countries depending on whether they include benefits or not *(NACIONAL SOBRE SIDA GRUPO DE EXPERTOS PrEP, 2018)*.

Included in the benefits		**Not included in benefits**	
Country	**Record Situation**	**Country**	**Record situation**
USA	April 2012. Daily use	**Belgium**	Approved EU August 2016 only daily use. Start June 2017
Southafrica	November 2015. Daily use	**Luxembourg**	Approved EU August 2016 only daily use. Intermittent start
Kenya	December 2015	**Thailand**	Submission for approval in 2014. Daily use
Canada	February 2016. Daily use	**Peru**	April 2016. Daily use
Israel	February 2016	**Australia**	May 2016. Daily use
France	Approved EU August 2016 only daily use. Start January 2016 by Temporary Authorization of Use for daily and intermittent use	**Sweden**	One monthly pack available per person
Norway	Approved EU August 2016 only daily use. Start October 2016	**UE countries**	Approved EU August 2016 only daily use: Austria, Bulgaria, Cyprus, Czech Republic, Croatia, Denmark, Slovakia, Slovenia, Spain, Estonia, Finland, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, Poland, Portugal, United Kingdom, Romania and Sweden

2.1.8 HIV prevention

There are many methods to prevent HIV today. In addition to limiting the number of sexual partners, not sharing needles, and using correct protection, newer medications can also be made, such as pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP).

a. Pre-exposure prophylaxis (PrEP)

PrEP is a biomedical intervention aimed at preventing HIV transmission in people who are seronegative for HIV at high risk of infection. The guideline approved by the European Medicines Agency (EMA) consists of the daily use (one pill once a day) of an antiretroviral medicine (Tenofovir disoproxil fumarate (TDF) + Emtricitabine (FTC), sold under the name Truvada®) (Table 2.1-4) (Nacional Sobre Sida Grupo De Expertos Prep, 2018), exposure to the virus, and should be accompanied by a package of preventive measures to improve adherence and influence the adoption of lower-risk behaviors.

PrEP, understood as the daily or intermittent administration of antiretrovirals to people who are not infected, but at high risk of contagion, represents an interesting strategy for the prevention of HIV transmission, especially sexually.

Most studies have shown an 86% efficacy. These results are closely linked to the level of adherence of treatment. The use of PrEP involves clinical and analytical follow-up along with assisted advice and adherence control. Most studies recommend following up for a year. Subsequently, the discontinuity of PrEP will be assessed, a re-evaluation planned and referrals to community or support programs established.

According to the article (Ferrández and Sesmero, 2016), the characteristics that an ideal agent should meet, include safety in chronic and episodic use in different populations, good penetration into target tissues, HIV activity, prolonged effect allowing for an assumed dosing regimen, high genetic barrier to the development of resistances, little potential for interaction, if possible, not part of existing treatment regimens, easy to use and of low economic impact.

After starting PrEP, clinical and analytical follow-ups should be performed every 3 months, re-testing the above tests.

Several cost-effective studies have been published in recent years. The results obtained depend on the type of model used, the parameters, the costs considered, and the population studied. However, they can all serve to draw general conclusions.

Chen and Dowdy (Chen and Dowdy, 2014) estimate that PrEP is more cost effective if used in groups with high prevalence and high adhesion, but decrease in groups of monogamous couples and serodiscordant couples when the HIV-positive person follows ART. On the other hand, other authors such as Ouellet et al. calculated that on-demand PrEP would save more costs over lives.

b. Post-exposure prophylaxis (PEP)

PEP is a preventive technique against HIV infection and should only be used in the event of an isolated and unusual occupational or non-occupational exposure to HIV (Relación Con Vih and Vhc En Adultos Y Niños) (Cayetana Fdez-Setién Fdez). This technique involves administering ART within 72 hours(*Profilaxis posexposición (PEP) | Definición | infoSIDA*, no date) after possible exposure to HIV with the aim of reducing the chances of getting the infection.

The effectiveness of PEP has been demonstrated by scientific evidence in isolated cases of empirical administration in the 1980s and 1990s, through observational studies in people receiving treatment, in studies demonstrating the effectiveness of PEP in primates, and in studies showing decreased vertical transmission in newborns from HIV-infected mothers.

Post-exposure prophylaxis should never supplement primary HIV prevention and should only be considered in certain situations that occur sporadically. In addition to the lack of data on the effectiveness of antiretrovirals in these cases, it is necessary to take into account the side effects that these treatments entail, the possibility of a development of resistance to the treatment, and the importance of the patient's adherence to therapy (Almeda *et al.*, 2002).

The decision to administer antiretroviral treatment as post-exposure prophylaxis should be made by the doctor and the patient individually and jointly. Prophylaxis should be initiated as soon as possible, ideally within the first 6 hours. The period of time after exposure, within which treatment is advised, is 48 to 72 hours. The duration of treatment should be 28 days if the serological situation of the patient is known, as well as the number of CD_4 lymphocytes, the viral load of HIV and the creation of resistance at the start of treatment. (Cayetana Fdez-Setién Fdez) Because of the greater effectiveness of triple ART therapy than monotherapy, indications with three drugs are more likely to prevent HIV infection from exposure. The guideline for choosing PEP is to combine 2 ITIAN (TDF/FTC) associated with a third antiretroviral drug.

According to Pinkerton, S. D., Holtgrave, D. R. And Bloom, F. R. ,there are three levels of risk defined by the type of pathway or type of exposure. the most common cases of HIV transmission are done through sexual intercourse (Figure 2.1-7) or use of previously used syringes (Figure 2.1-8). In cases with appreciable risk, prophylaxis is recommended. In low-risk cases it could be considered, and in cases of minimal risk it should be discouraged.

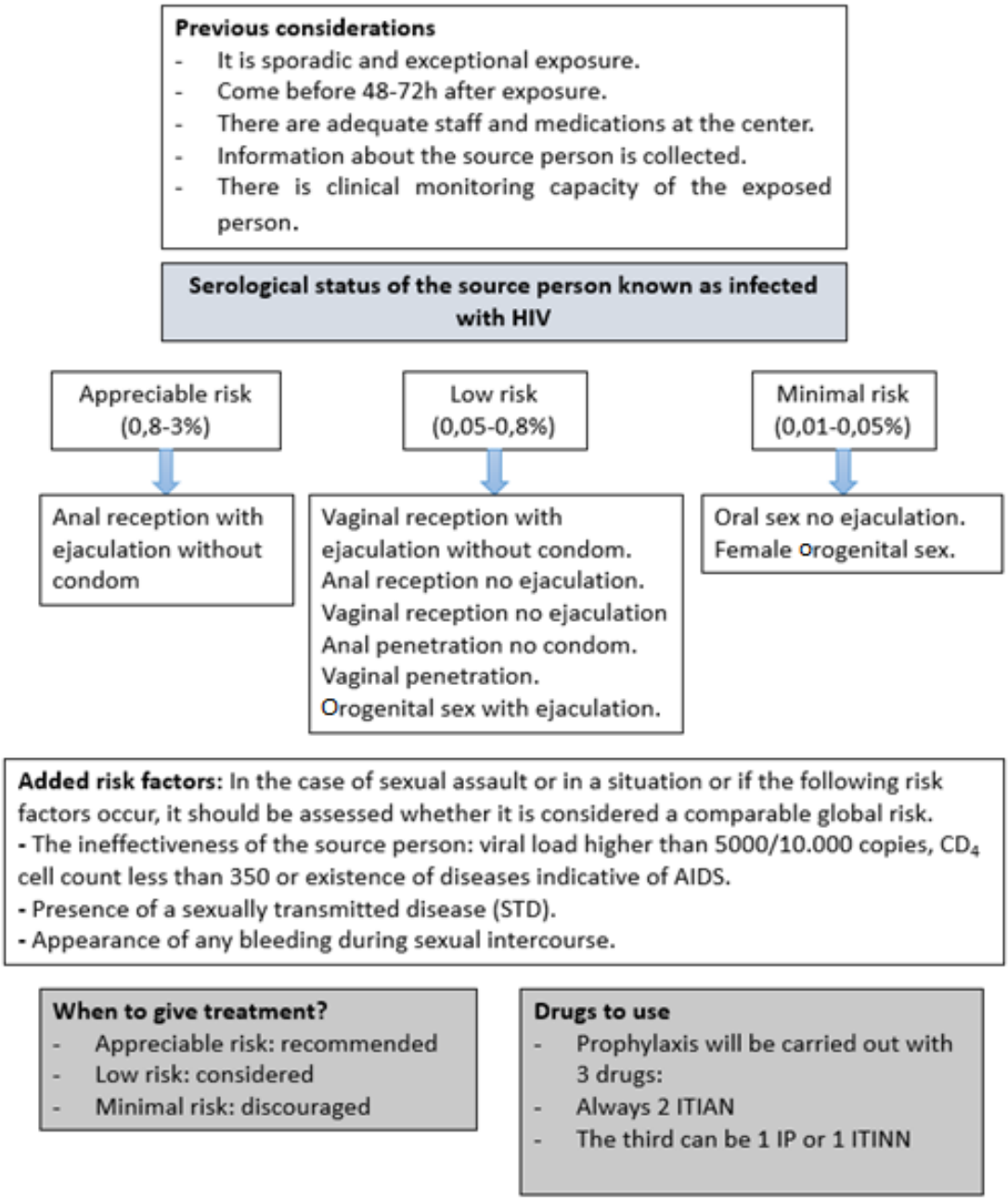


Figure 2.1-7 Prophylaxis Scheme: Sexual HIV Risk Assessment (Almeda *et al.*, 2002).

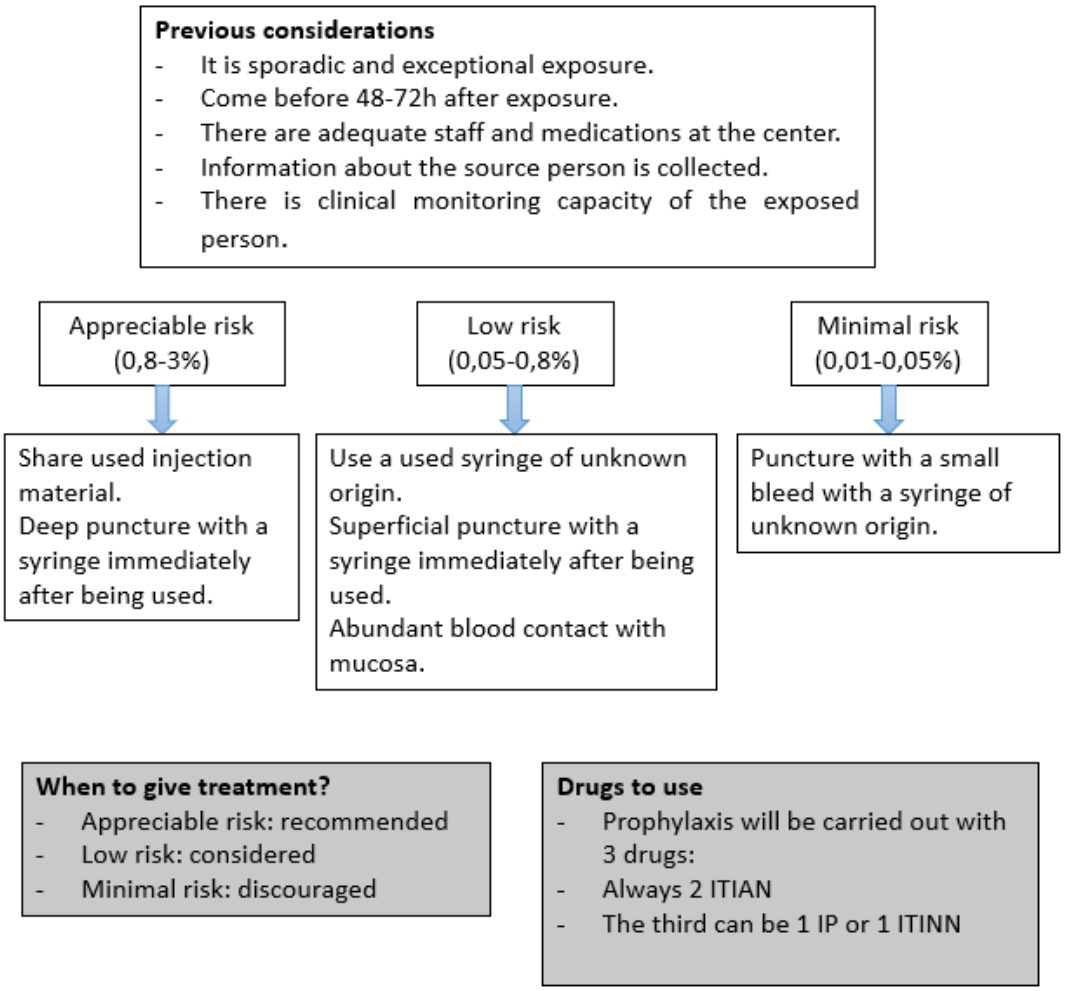


Figure 2.1-8 Prophylaxis scheme: assessment of the risk of HIV infection parenterally (Almeda *et al.*, 2002).

In relation to the cost effectiveness of PEP, as in the previous case of PrEP, it varies depending on the models studied, the parameters used, and populations of interest. Studies on PEP Pinkerton, S. D., Holtgrave, D. R. And Bloom, F. R. concluded that infected persons should be restricted to patients who have participated in receptive anal intercourse and in cases where there is any possibility of infection. On the other hand (Pinkerton *et al.*, 2004) ensured that the use of PEP was cost-effective by conventional standards and saved costs for people who perform male-male receptive anal intercourse.

2.1.9 HIV treatment

In 1987, the clinical use of zidovudine (ZDV) for the treatment of HIV infection was approved. This first antiretroviral drug (FARV) was followed by other nucleoside analog reverse transcriptase inhibitors (ITINs) that were first used individually and later in combinations. However, both drugs failed due to the development of resistance mutations towards these drugs. It was not until 1996 that the addition of a protease inhibitor (IP) to a pair of ITIAN that HIV replication was suppressed. Therefore, this combination of FARV and shortly thereafter the one formed by two ITINs and a non-nucleoside-analog reverse transcriptase inhibitor (ITINN) was called a "highly effective antiretroviral processing" (TARGA), which we will henceforth simply call antiretroviral processing (ART) (Table 2.1-5) (Lozano and Domingo, 2011).

Table 2.1-5 Pharmaceutical presentations with fixed-dose combinations of 2 or 3 antiretroviral drugs whose clinical use is approved in Spain. (Walmsley *et al.*, 2013)

ITIAN combinations	ITIAN and ITINN combinations
Zidovudine and lamivudine Abacavir and lamivudine Tenofovir and emtricitabine Zidovudine, lamivudine and abacavir	Efavirenz, emtricitabine and tenofovir

The goal of antiretroviral therapy is to prevent the virus from reproducing, reducing its viral load to undetectable levels in the patient. In other words, to levels below 50 copies/mL within 24 weeks after starting treatment. With less concentration of HIV, the immune system is more likely to recover. Although antiretrovirals do not remove the virus from the host organism, they act at different biological stages, limiting replication and thus prevent the deterioration of the patient's immune system. People with HIV should start antiretroviral processing as soon as possible, especially those who are pregnant, who have AIDS or certain HIV-related diseases and co-infections. This also applies to individuals with early HIV infection (Lozano and Domingo, 2011).

Before performing antiretroviral processing, it is appropriate to know the clinical and biological parameters of the patient in order to be able to evaluate it (Table 2.1-6). The best marker of the

risk of clinical progression of HIV infection is the CD_4^+ lymphocyte count. Plasma viral load should also be determined, as this is a decisive factor in initiating ART.

Table 2.1-6 Clinical and biological parameters to be evaluated before initiating antiretroviral processing (Lozano and Domingo, 2011).

Physical scan: It should be as complete as possible, including height, weight, blood pressure and abdominal perimeter.

Laboratory tests:
• CD_4^+ lymphocyte count and percentage.
• Plasma viral load.
• Plasma biochemical parameters:
  ○ Creatinine, sodium, potassium, calcium, and phosphate.
  ○ ALT, AST, GGT, total bilirubin, alkaline phosphatase, LDH.
  ○ Basal glucose, cholesterol, and triglycerides.
• Urine: proteinuria and glycosuria and sediment.
• Blood count:
  ○ Hemoglobin/hematocrit.
  ○ Leukocyte formula and count.
  ○ Platelets.
• HBV and HCV serological markers, if not previously made.
• A genomic test of resistance.
• HLA-B 5701.
• Pregnancy test in women of fertile age in which it is considered the use of efavirenz.

Indirect estimates: • Glomerular filtering • Cardiovascular risk

Several studies have shown that CD_4^+ cell recovery was superior when raltegravir was administered compared to efavirenz when combined with tenofovir/emtricitabine in HIV-1 infected individuals using ART (Rockstroh JK, 2011). Raltegravir had a lasting viral suppression and a great immune restoration.

Other studies have shown that people infected with HIV-1 who received dolutegravir-abacavir-lamivudine (DTG-ABC-3TC) had a shorter mean time for viral suppression, as well as increases in CD_4^+ cell counts compared to those receiving efavirenz-tenofovir disoproxil fumarate-emtricitabine (EFV-TDF-FTC) (Walmsley *et al.*, 2013).

(Tanuma *et al.*, 2017)reported that stavudine-based regimens (d4T or AZT) and nevirapine-based regimens (NVP or EFV) were associated with impaired immune recovery.

In addition, a study by Zhang et al. showed that immune recovery with AZT was higher compared to patients with TDF-containing regimens.

Currently, there are many medicines available for HIV treatment, these are grouped into 7 different classes and are differentiated by the way they fight the infection.

The selection of a regimen for HIV treatment depends on different factors, such as side effects and possible drug interactions, which is why there are a wide variety of regimens to choose from. (R. Rubio *et al.*, 2010) These include:

- Reverse transcriptase inhibitors analogous to nucleosides and nucleotides (ITINs)

Their main function is to block reverse transcriptase, an enzyme that needs HIV to reproduce. Currently we can find the following drugs that carry it out: AN: zidovudine (ZDV), didanosine (ddI), emtricitabine (FTC), lamivudine (3TC), stavudine (d4T) and abacavir (ABC). A nucleotide analogue, tenofovir (TDF) is also available. These drugs need to be activated by incorporating three phosphate molecules in order to act by inhibiting reverse transcriptase. These reactions are catalyzed by cellular enzymes that are usually and may be different for each compound and for each cell type. Therefore, despite having a very similar chemical structure and mechanism of action, they behave like different drugs and the combination of two or more can be potentially synergistic or additive and expand on the spectrum of infected cells of the host on which they exercise their activity.

On the other hand, Tenofivir is a nucleotide analogue, it also requires phosphorylation, but in this case, it only needs two phosphate molecules. They act through a double mechanism: by competition with natural nucleotides in their incorporation into the nascent DNA chain generated by IT and as "chain terminators" in the synthesis of viral genomic DNA.

- Non-nucleoside reverse transcriptase inhibitors (ITINN)

The nucleosides marketed in our country are: efavirenz (EFV), nevirapine (NVP) and etravirine (ETR). This family of drugs does not work against type HIV-2 or group O of HIV-1 because the reverse transcriptase of these viruses has natural resistance to existing nucleosides.

- Protease inhibitors (IP)

IPs (atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, saquinavir, RTV and tipranavir) work by inhibiting HIV protease. They do not need to be transformed or metabolized to be active and act in the final phase of the viral replication cycle. IPs bind to the catalytic site configured by the 2 monomers that make up HIV protease by blocking the action of the enzyme that processes gag/pol precursor polyproteins in their final products.

- Fusion inhibitors

HIV penetration into the cell begins when the gp120 binds to the CD_4 molecule of the target cell, as well as to the coreceptors. The viral gp41 then experiences an alteration in its conformation that allows the fusion of viral and cell membranes.
The drug best known to be a fusion inhibitor is Enfuvirtide, a synthetic peptide that prevents the formation of a six-propeller structure that is essential for membrane fusion.

- Integrase inhibitors

Integrase is one of the most important enzymes that HIV needs to reproduce within human cells. After HIV enters the cells it is this enzyme, the integrase, which gets the genetic material of the virus so that it joins the genetic material of the human cell. (Castro, 2007)

Integrase inhibitors are a new family of antiretroviral drugs, used in both HIV-1 and HIV-2. They are used on patients who have never received antiretroviral processing or who have failed with multiple previous drugs. Integrase inhibitors work by altering the molecules of the viral integrase, so that it no longer can bind the reactive ends of viral DNA to cell DNA. Integrase inhibitors include RAL and elvitegravir. Integrase is a viral enzyme that has no analogues in the human cell and is therefore expected that its inhibition does not cause any significant alteration in host cells and its potential toxicity is low.

- Post-fixation inhibitors

Post-fixation inhibitors are a type of medications that bind to the CD_4 receptor of a host CD_4 lymphocyte. This prevents HIV from attaching to the CCR5 and CXCR4 coreceptors and entering the cell.

- Pharmacokinetic enhancers

They are a class of medicines used to strengthen the effectiveness of another medicine. Both are administered together. The enhanced pharmacokinetics block the breakdown of the second in the blood, thus increasing its amount. The drug best known as pharmacokinetic enhancer is Ritonavir.

2.2 HIV epidemiology

2.2.1 Importance and history of epidemiology

Epidemiology attempts to define what the total number of infected will be or what the maximum number of infected will be at a precise time, moreover, it studies the disease behavior. It also tries to answer questions of why epidemics do not infect entire populations, being that there are people resistant to these diseases.

Mathematics plays the most important role in epidemiology. The first published work using statistical enumeration was published in 1747 by James Lind, where he demonstrated that scurvy disease was caused by poor citrus consumption. The second work was published in 1760 by Daniel Bernouilli, consisting of a model for smallpox in which it demonstrated how vaccination, based on the inoculation of pus in the body, was effective for healthy people.

However, it was not until the 20th century that William Heaton formed a discrete model analyzing the measles epidemic in England, taking into account the density of infected individuals within a healthy population. At this point, deterministic modeling in epidemiology really began to develop.

Since then, there have been multiple models that have made great strides, including the formulation of malaria transmission by Ronald Ross or the study on the relationship between tobacco use and cancer of the oral cavity by Bigelow and Lombard.

2.2.2 HIV in the world

The United Nations AIDS program (López, S., Garrido, F., Hernández, M. (2000)) estimates that in 2018 the number of people living with HIV was 37.9 million (Figure 2.2-1), of which only 24.5 million had access to antiretroviral therapy, 770000 died of AIDS-related diseases and 1.7 million contracted AIDS at the end of 2018.

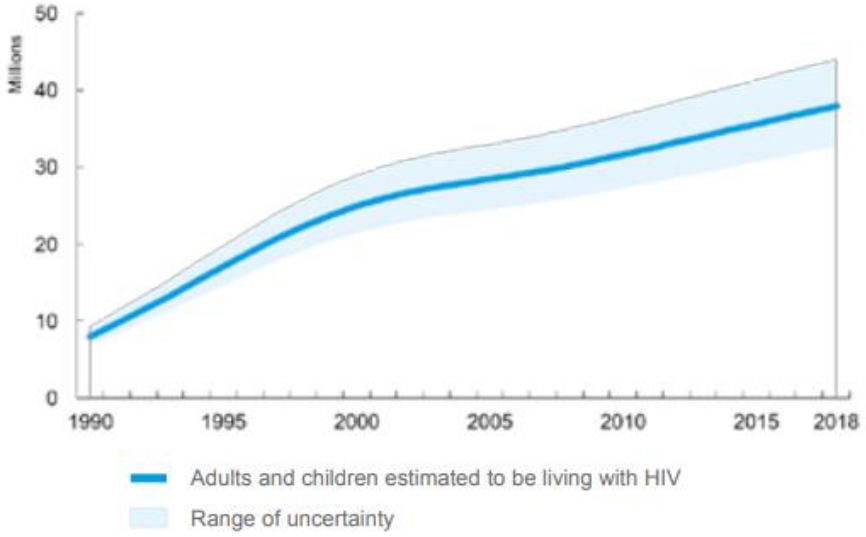


Figure 2.2-1 Adults and children estimated to be living with HIV 1990-2018 (*HOJA INFORMATIVA-DIA MUNDIAL DEL SIDA 2019*).

In total, we have 74.9 million people infected since the beginning of the epidemic, of which 32 million have died from related diseases. In 2018, a study was conducted that found the number of people living with HIV is of 37.9 million of whom 1.7 million are children under the age of 15. 79% of all people living with HIV knew their serological status and about 8.1 million did not know they were living with the virus.

In recent years, there has been an increase in access to antiretroviral therapy. At the end of June 2019, 24.5 million had access, in 2018, 23.3 million, and in 2010 7 million had access to therapy In 2018, 62% of all people living with HIV had access to treatment.62% of adults over the age of 15 had access, as well as 54% of children up to 14 years old. 68% of adult women over the age of 15 had access to treatment, however, only 55% of adult men over the age of 15 had it. In 2018, 82% of pregnant women living with HIV had access to antiretroviral drugs to prevent transmission of the virus to their children.

Since the peak of 1997, new HIV infections have reduced by 40%. Since 2010, new HIV infections have fallen by about 16% from 2.1 million to 1.7 million in 2018 (Figure2.2-2). HIV infections in children in 2018 also fell by 41%, from 280000 in 2010 to 160000 in 2018.

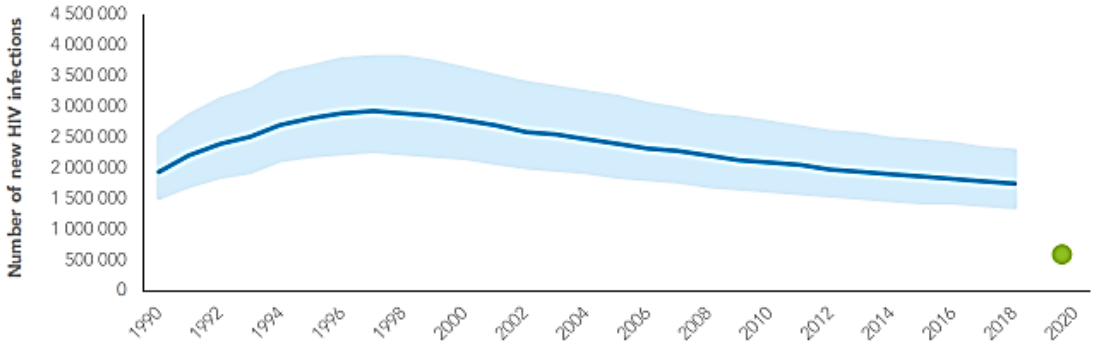


Figure 2.2-2 Number of new HIV infections, global, 1990-2018 and 2020 target (*HOJA INFORMATIVA-DIA MUNDIAL DEL SIDA 2019*).

Since the peak of 2004, cases of AIDS-related deaths have been reduced by more than 56% (Figure 2.2-3).

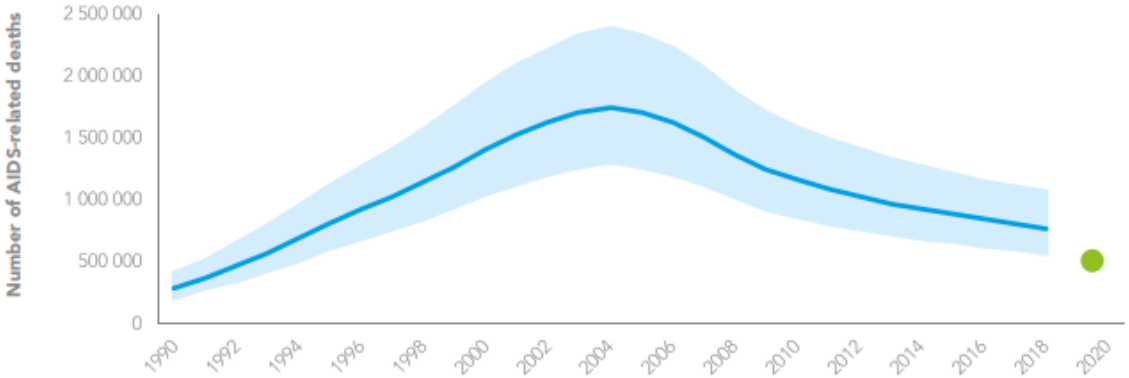


Figure 2.2-3 Number of AIDS-related deaths, global, 1990-2018 and 2020 target (*HOJA INFORMATIVA-DIA MUNDIAL DEL SIDA 2019*).

The area most affected by the human immunodeficiency virus is sub-Saharan Africa with a total of 20.6 million people living with the virus. Compared to the rest of the regions, we can say that half of the reported HIV cases are in eastern and south Africa. (Table 2.2-1)

Table 2.2-1 Regional HIV and AIDS statistics and features 2018 (*HOJA INFORMATIVA-DIA MUNDIAL DEL SIDA 2019*).

	Adults and children living with HIV	Adults and children newly infected with HIV	Adult and child deaths due to AIDS
Eastern and southern Africa	20.6 million [18.2 million–23.2 million]	800 000 [620 000–1.0 million]	310 000 [230 000–400 000]
Western and central Africa	5.0 million [4.0 million–6.3 million]	280 000 [180 000–420 000]	160 000 [110 00–230 000]
Middle East and North Africa	240 000 [160 000–390 000]	20 000 [8500–40 000]	8400 [4800–14 000]
Asia and the Pacific	5.9 million [5.1 million–7.1 million]	310 000 [270 000–380 000]	200 000 [160 000–290 000]
Latin America	1.9 million [1.6 million–2.4 million]	100 000 [79 000–130 000]	35 000 [25 000–46 000]
Caribbean	340 000 [290 000–390 000]	16 000 [11 000–24 000]	6700 [5100–9100]
Eastern Europe and central Asia	1.7 million [1.5 million–1.9 million]	150 000 [140 000–160 000]	38 000 [28 000–48 000]
Western and central Europe and North America	2.2 million [1.9 million–2.4 million]	68 000 [58 000–77 000]	13 000 [9400–16 000]
TOTAL	37.9 million [32.7 million–44.0 million]	1.7 million [1.4 million–2.3 million]	770 000 [570 000–1.1 million]

2.2.3 Eastern and southern Africa

Most of the world's cases are in sub-Saharan Africa with a total of 20.6 million and 800000 new infected ones per year. (Figure 2.2-4)

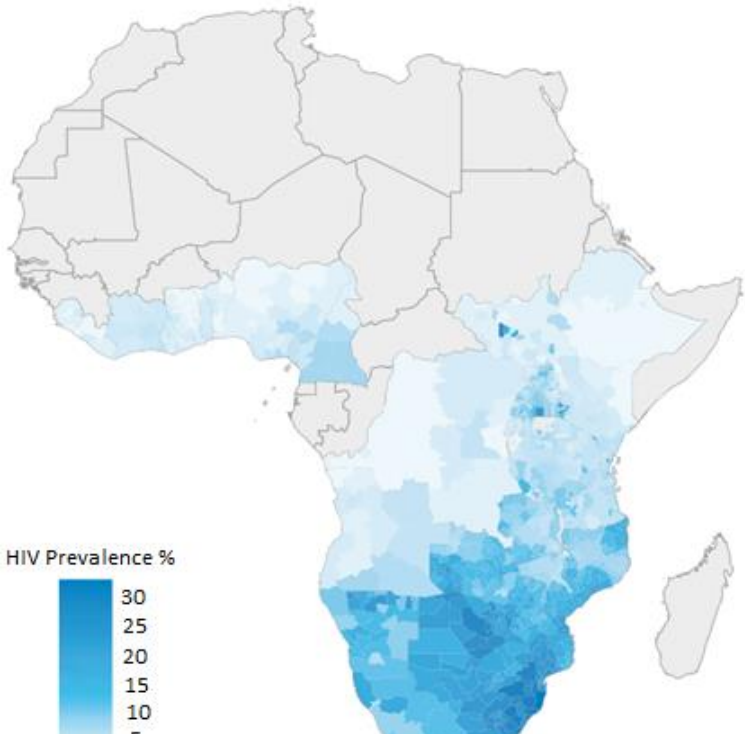


Figure 2.2-4 HIV prevalence, adults (aged 15-49 years) 2018 (Unaids, 2019).

In 2018, 800000 people were estimated to have contracted HIV, resulting in a 28% decrease in the number of new infected people since 2010 (Figure 2.2-5). Young women aged 15 to 24 accounted for 26% of new infections and an estimated quarter of new infections were among key populations and their sexual partners (Figure 2.2-6). Several countries showed sharp declines in infected people between 2010 and 2018 such as Comoros, Rwanda, South Africa and Uganda, but new infections increased in other countries, such as Angola, Madagascar and South Sudan. (Figure 2.2-7)

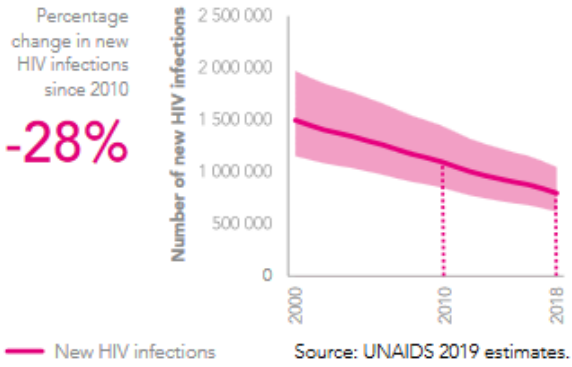


Figure 2.2-5 Number of new HIV infections, eastern and southern Africa, 2000-2018 (Unaids, 2019).

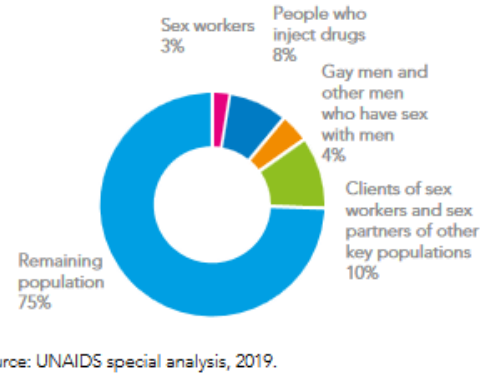


Figure 2.2-6 Distribution of new HIV infections (aged 15-49 years), by population group, eastern and southern Africa, 2018 (Unaids, 2019).

Figure 2.2-7 Percentage change in new HIV infections, by country, eastern and southern Africa, 2010-2018 (Unaids, 2019).

In 2018, there were 310000 AIDS-related deaths, a 44% decrease since 2010. Five cities had a drop in AIDS-related deaths of more than 50% over the past 8 years: Kenya, Malawi, South Africa, Uganda and Zimbabwe. The region's prevalence-incidence index was 3.9% in 2018, a significant decrease of 6.5% in 2010 (Figure 2.2-8).

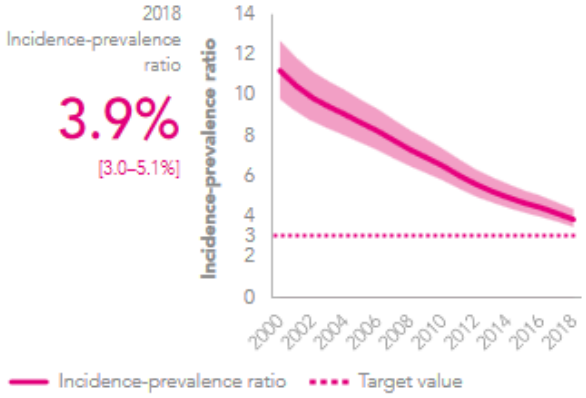


Figure 2.2-8 Incidence-prevalence ratio, eastern and southern Africa, 2000-2018 (Unaids, 2019).

Of the 20.6 million people living with HIV in sub-Saharan Africa, the proportion of HIV in sub-Saharan Africa increased from 77% in 2015 to 85% in 2018. It is estimated that 67% of people living with HIV were on treatment compared to 53% in 2015.

An estimated 84000 people in the region took pre-exposure prophylaxis (PrEP) at least once in 2018. 37% of these people resided in Kenya. Effective expansion of PrEP requires attracting people at high risk of HIV infection, supporting proper use and adherence, and strengthening other aspects of sexual and primary health care.

The prevalence of male circumcision is high in countries and provinces prioritized for voluntary medical male circumcision (VMMC). More than 70% of adult men (aged 15 to 49) are circumcised in Ethiopia's Gambela region, Lesotho, Kenya's Nyanza Province and the United Republic of Tanzania. In Zimbabwe, fewer than one in four adult men was circumcised.

About eight out of ten sexually active teens and young men reported having sex with a non-marital partner in the past year. In most countries, very few young people reported using condoms during

a higher-risk sexual relationship. A higher proportion of young men than young women reported having sex before the age of 15.

Each week, around 6200 young women between the ages of 15 and 24 get HIV infection. In sub-Saharan Africa, four out of five new infections in adolescents between the ages of 15 and 19 are women.

HIV infection tends to occur more in developing countries, due to limited information and knowledge about the disease. This is joined by rape cases and sexual practices.

2.2.4 Western and central Europe

The estimated number of new HIV infections has declined over the past decade in Western and Central Europe. Reductions in AIDS-related deaths have been strongest, reaching 13000 in 2018. (Figure 2.2-9). The region's incidence-prevalence ratio has decreased to 3.1% in 2018. (Figure 2.2-10). According to data from UNAIDS, Denmark, Norway, Portugal and Spain have managed to reduce the number of annual infections, while Bulgaria, the Czech Republic, Poland and Slovakia have seen HIV infections hastily increased. (Figure 2.2-11).

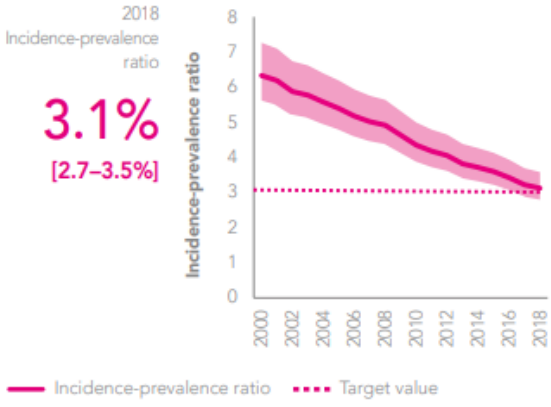


Figure 2.2-9 Incidence-prevalence ratio, western and central Europe, 2000-2018 (Unaids, 2019).

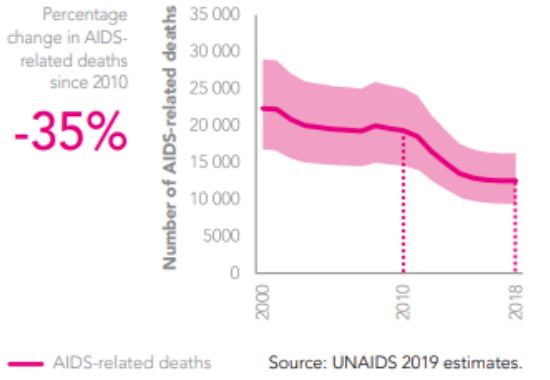


Figure 2.2-10 Number of AIDS-related deaths, western and central Europe, 2000-2018 (Unaids, 2019).

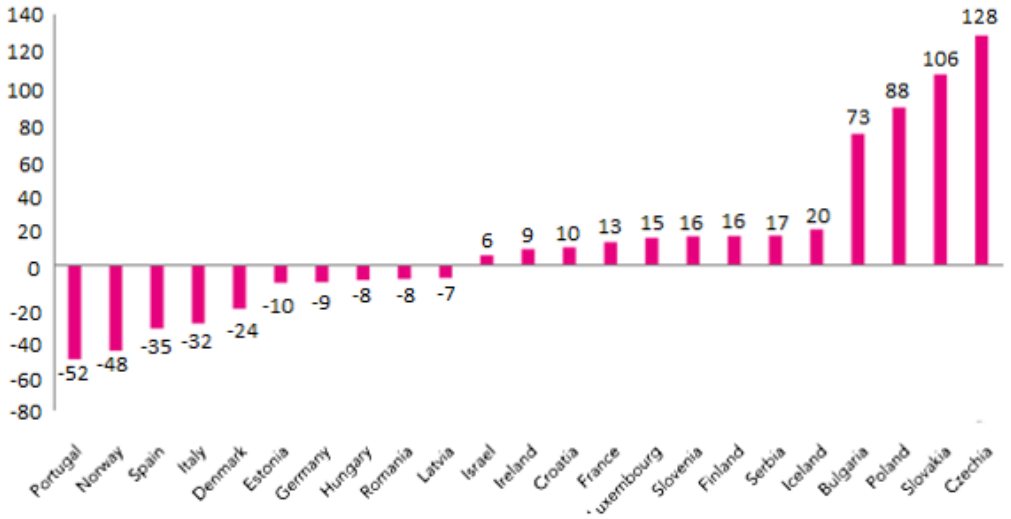


Figure 2.2-11 Percentage change in new HIV infections, by country, western and central Europe, 2010-2018 (Unaids, 2019).

Key populations and their partners make up 88% of HIV infections in 2018 with more than half of them being gay men or men who have had sex with other men (Figure 2.2-12). There is a difference in diagnostics between western and central Europe.

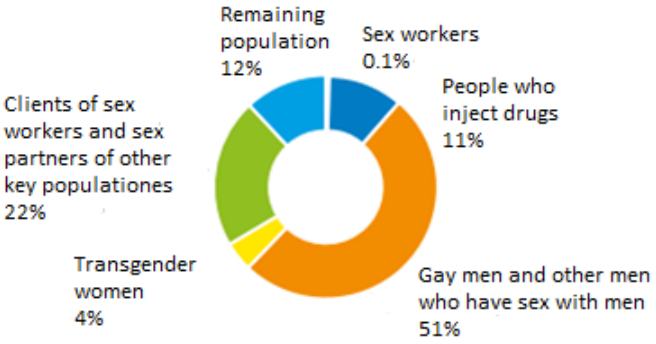


Figure 2.2-12 Distribution of new HIV infections (aged 15-49 years), by population group, western and central Europe, 2018 (Unaids, 2019).

The average prevalence of HIV among gay men and men who have had sex with other men within the 21 countries studied is 6.7%, with six of those countries having a prevalence of 10%. New HIV diagnoses among people who inject drugs have declined in Western and Central Europe, accounting

for only 11% of all new diagnoses of the virus. On the other hand, of the approximately 2.2 million people living with HIV in 2018, 88% knew their condition, 79% were being treated and 64% achieved viral suppression (Figure 2.2-13). With the results obtained it can be said that progress seems to be on track to meet the target 90-90-90.

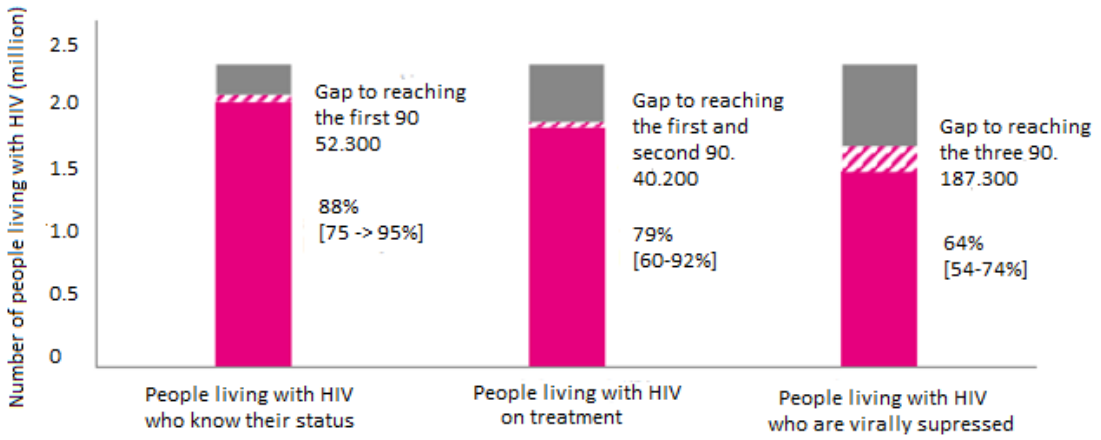


Figure 2.2-13 HIV testing and treatment cascade, western and central Europe, 2018 (Unaids, 2019).

Late HIV diagnosis remains a challenge in Western and Central Europe. Among newly diagnosed adults (15 years and older), just over half (53%) were late presenters, with CD_4 cell counts less than 350 cells/mm^3, including those with advanced HIV infection, in other words, a CD_4 cell count of less than 200 cells/mm^3 (32%). The percentage of late presenters was higher for heterosexual people (62% for men and 54% for women) and for people who acquired HIV through injectable drug use (55%). On the other hand, it was smaller for gay men and men who have sex with other men (39%). Of infected people aged 15 to 19, 34% were diagnosed late, the same was the case for 32% of those infected between the ages of 20 and 24 and 66% for people over the age of 50.

2.2.5 Epidemiology in Spain

The number of new HIV infections in Spain in 2018 was 3244 (*Vigilancia Epidemiológica Del Vih Y Sida En España 2018*), a 35% decrease compared to the 4700 infected in 2010. Fewer than 100 people infected with the virus were between 0 and 14 years old, less than 500 people were women over the age of 15, and finally 2700 of the new infections were adult men over the age of 15. Transmission between men who have sex with other men was the most common being 54% of infections, followed by heterosexual transmission that involved 26.7% and finally, people who inject

drugs made up about 3.2% (Figure 2.2-14). Therefore, 83.1% of new HIV diagnoses in 2018 were sexually transmitted.

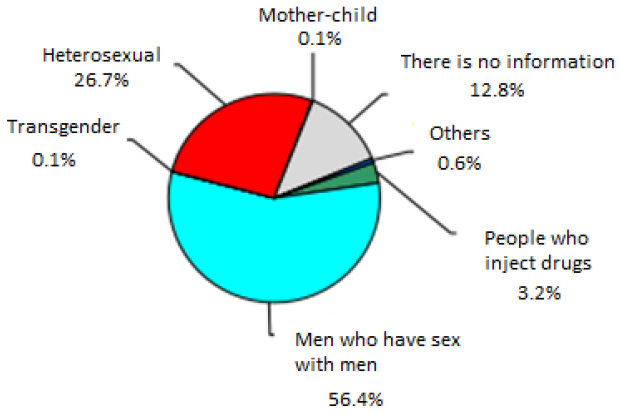


Figure 2.2-14 New HIV diagnoses. Distribution by transmission mode Spain, year 2018 (Vigilancia Epidemiológica Del Vih Y Sida En España 2018)

In 2018, 37.6% of new HIV diagnoses were made in people from other countries. After the Spanish, the most frequent origin was Latin American with 21.7% (Figure 2.2-15). In the case of women, 56.1% of the diagnoses were born outside Spain.

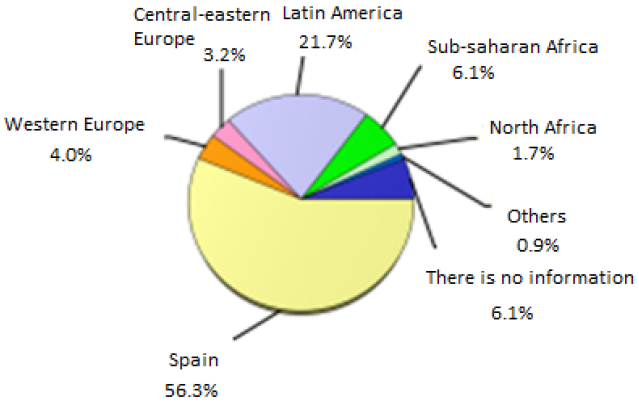


Figure 2.2-15 New HIV diagnostics. Distribution by geographical area of origin. Spain, year 2018 (Vigilancia Epidemiológica Del Vih Y Sida En España 2018)

Nowadays in Spain, there are 150,000 people living with HIV, most of whom are adult men over 15 years old covering a number of 120,000 people. The second most affected group are women over the age of 15 with a number of 27,000 people infected, and finally, under the age of 14 involving less than 100 cases.

2.2.6 Epidemiology in Catalonia

The HIV diagnoses reported in Catalonia in 2018 were 613 (Figure 2.2-16), which represents a rate of 8.1 cases per 100.000 inhabitants. Most of these cases were men who accounted for 87% of diagnoses (Figure 2.2-17) (Vigilància epidemiològica de la infecció pel VIH i la SIDA a Catalunya, 2019) . The average age of the cases was 36 years old. 44% of these cases were diagnosed in people born outside the Spanish state. Of the total, 62% belonged to people from Latin American and Caribbean countries.

More than half of the diagnoses with 59% were among men who have sex with other men, with 14% were diagnosed in heterosexual men and with 9% heterosexual women. Of the total HIV diagnoses in 2017, 83% had information on CD4 lymphocyte count of which 44% of these cases had late determination. The late detection ratio was higher in heterosexual and younger men and women in gay men.

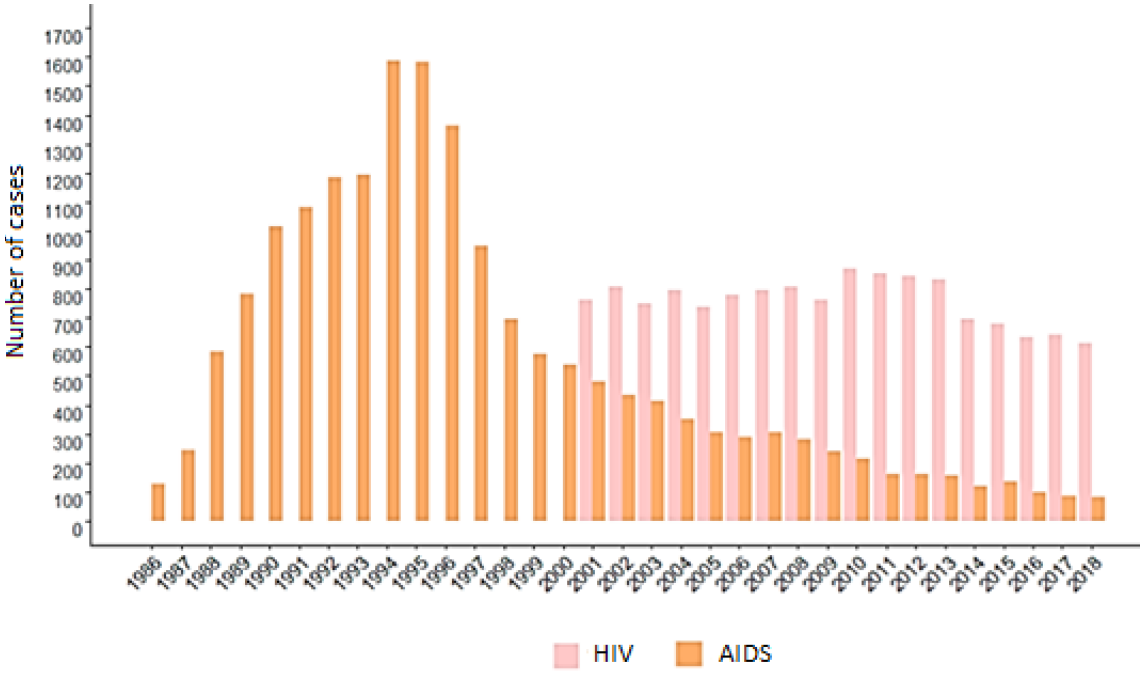


Figure 2.2-16 Annual evolution of HIV diagnoses and AIDS cases in Catalonia, 1981-2018 (*Vigilància epidemiològica de la infecció pel VIH i la SIDA a Catalunya*, 2019).

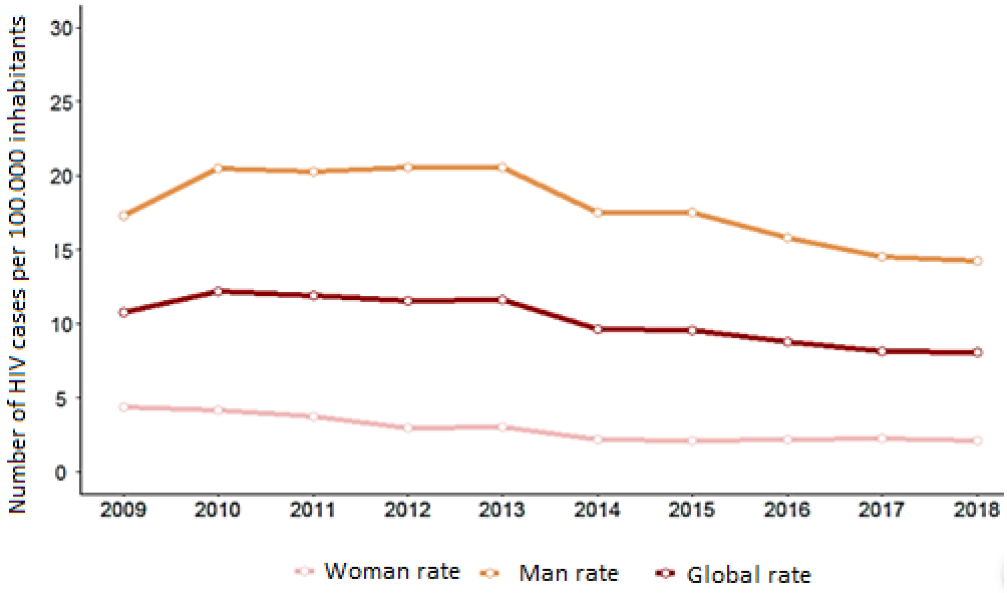


Figure 2.2-17 Evolution of HIV diagnoses per 100,000 inhabitants according to sex in Catalonia, 2009-2018 (*Vigilància epidemiològica de la infecció pel VIH i la SIDA a Catalunya*, 2019).

2.3 Final HIV discussion

Having studied the natural history of the human acquired immunodeficiency virus and its global and regional epidemiology, we can conclude that it remains one of the major problems in society, especially in developing regions such as sub-Saharan Africa, where HIV continues to grow uncontrollably and AIDS continues to cause thousands of deaths a year.

The most important reasons why the virus affects these communities the most are mainly a lack of resources, as well as poor management in public health.

Developed regions such as Central Europe or the United States of America have fewer infected populations, yet a cure for eliminating the virus has not yet been found. That is why we can say that we are still far from being able to find a drug that is totally effective in combating this illness because its behavior is different depending on the person and its replication rate is very high. One of the improvements that have been made in recent years, is the use of different techniques that allow us a faster and more accurate diagnosis and that is why it allows us to identify the virus in its initial phases and thus be able to fight it in the most effective way. Thus, avoiding its advanced late detection, which would be a difficulty in improving the AIDS disease. As is the case of fourth generation ELISA, which allows us to detect in the first 15 days after being exposed to the virus.

3 Bibliographic review. Mathematical models

3.1 Mathematical models in epidemiology

A model is the simplified representation of a system or a process. If you know the internal processes and the relationships between them, then it is possible to know the equations that describe which we call a mathematical model. The degree of effectiveness will depend on the knowledge available and the possibilities of experimentation.

To build a mathematical model it is necessary to take into account two phases, abstraction and interpretation. The first phase needed to build a mathematical model is abstraction. For this you have to establish certain hypotheses, define variables, and develop the appropriate mathematical equations to solve the problem. The following steps are to simplify the tools used, collect situational data, and compare it with predictions.

Early mathematical models allowed the study of simple diseases, as knowledge increased and models were improved, they would include other important parameters, such as the dynamics of infection of the virus or the behavior of different populations. Today, multiple complex mathematical models are made that allow great advances in epidemic control and prevention.

3.1.1 Classification of models

The classification of the models depends on certain characteristics and the purpose of the study. Therefore, the models need to be classified according to the principles of (Haefner, 2005). A model can belong to more than one of these classes:

- Mechanistic models: those that are built from a set of hypothesis about the dynamics of the system (*mecanicismo | Diccionario de la lengua española | RAE - ASALE*).
- Empirical models: they are descriptive models whose behavior derives from pure observation of data.
- Dynamic models: behavior of the system is studied over time.
- Static models: they do not depend on time or are associated with a balance point.
- Continuous models: the evolution of the state of the system is continuous or over time.

- Discrete models: processes modelling is built at discrete time steps and/or with a discrete spatial approach.
- Stochastic models: they depend on a random factor or deterministic factors that the model does not contemplate or cannot describe.
- Deterministic models: the result of the model depends only on input factors that can be adjusted and defined.

Usually in epidemiology, two types of dynamic mathematical models are used. On the one hand, there are individual-based models (IBM), which are discrete and mechanistic models with a strong stochastic component, in which the behavior of each individual is studied. Then there are the compartmental models. These models are usually deterministic, and individuals are considered to belong to a set which has a particular average state. Finally, we have the hybrid models that are those that mix the previous two.

3.1.2 Individual-based models

Individual-based models (IBM) are bottom-up computational representations of systems that are characterized in the construction of models based on the identification of entities involved in the system, agents, and the interactions that occur between them.

These represent the behavior of an individual, their interactions with other individuals, and with their environment, taking into account that which it aims to study. This data is then recorded on a computer where we can study, through evolutionary simulations, how these individuals interact. Each individual has its own characteristics (sex, age, mass, size or volume...) and rules of behavior (movement, metabolization, mutation, aging, death...).

One of the complexities that IBMs have is that they deal with many variables, parameters, and rules that apply to different features at different spatial scales, making them less manageable than many analytical models.

3.1.3 Compartmental models

Compartmental models are usually deterministic models in which individuals belonging to a model compartment are considered to be an assembly, rather than being considered individually. Each

compartment depends on the average conditions of the individuals. Compartmental models are often used in the study of large populations.

The acronym for different epidemiological models are based on flow patterns between the compartments: SI, SIS, SEI, SIX, SIR, SIRS, SEIR, SEIRS, MSEIR, MSEIRS.

The simplest epidemiological models are (María González *et al.*, 2017):

- SIS: Recovery does not provide immunity. Individuals go from susceptible to infectious and again susceptible.
- SIR: Individuals recover with permanent immunity.
- SIRS: Individuals recover with temporary immunity, so that they are re-susceptible.
- SI: Individuals do not recover.

In these models described above, a population division is based on three classes that vary over time. Susceptible (S), infected (I) and recovered (R). Diseases caused by a virus are usually of the SIR type, while diseases caused by bacteria are of the SIS type.

a. SI model

The SI model is the simplest possible. The population consists only of susceptible (S) and infected (I) individuals, if an individual is infected, the disease is permanent, and therefore there is no chance of recovery (Figure 3.1-1).

Figure 3.1-1 SI model flowchart. Susceptible- Infected (María González et al., 2017).

This model consists of a system of two differential equations that show the number of people susceptible S(t) and infected I(t) as time-dependent variables. According to the mass action law, the change from susceptible to infected is proportional to the size of the populations.

$$\frac{dS}{dt} = -\beta \cdot S(t) \cdot I(t), \quad S(0) = S0 > 0 \qquad (3.1)$$

$$\frac{dI}{dt} = \beta * S(t) * I(t), \quad I(0) = I0 > 0 \qquad (3.2)$$

b. SIR model

This model considers only three classes of individuals (Figure 3.1-2):

- S (t) represents susceptible individuals, those who have not yet been infected.
- I (t) represents infected individuals who can transmit the disease.
- R (t) represents recovered individuals who have suffered the infection and create temporary or permanent immunity.

Figure 3.1-2 SIR Model Flowchart (Susceptible – Infected – Recovered) (María González et al., 2017).

The simplest SIR model was proposed by Kermack and McKendrick in 1927 and can be formulated as the following system of differential equations:

$$\frac{dS}{dt} = -\beta * S(t) * I(t) \;\; S(0) = S0 > 0 \qquad (3.3)$$

$$\frac{dI}{dt} = \beta * S(t) * I(t) - \gamma * I(t) I(0) = I0 > 0 \qquad (3.4)$$

$$\frac{dR}{dt} = \gamma * I(t) \;\; R(0) = 0 \qquad (3.5)$$

Where S(t), I(t) and R(t) corresponds to the number of individuals in the susceptible, infected and recovered classes, respectively, at time t. β is the parameter related to the rate of infection and γ is the parameter related to the cure rate.

c. SIR model with births and deaths

This model is an extension of the previous considering that individuals can be born and die. This model is determined by the following differential equations - where N is the total population, in other words, the sum of the susceptible, infected and recovered people (N-S+R+R), β is the rate of infection, μ is the average rate of births and deaths from natural causes, and γ is the rate of infection.

$$\frac{dS}{dt} = -\beta * S * I + \mu(N - S) \qquad (3.6)$$

$$\frac{dI}{dt} = \beta * S * I - \gamma * I - \mu * I \quad (3.7)$$

$$\frac{dR}{dt} = \gamma * I - \mu * R \quad (3.8)$$

d. SIRS model

This model is an extension of the SIR model, where recovered individuals lose immunity and return to the susceptible state (Figure 3.1-3).

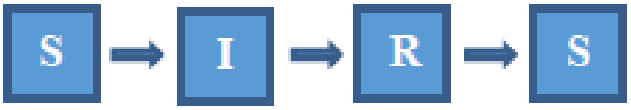


Figure 3.1-3 SIRS Susceptibles- Infected- Recovered-Susceptibles model flowchart (María González et al., 2017).

The model is defined according to the following equations, where N would be the total population, β rate of infection, μ the average rate of births and deaths from natural causes, γ the rate of infection and finally f the rate of loss of immunity.

$$\frac{dS}{dt} = -\beta * S * I + f * R \quad (3.9)$$

$$\frac{dI}{dt} = \beta * S * I - \gamma * I - \mu * I \quad (3.10)$$

$$\frac{dR}{dt} = \gamma * I - \mu * R - f * R \quad (3.11)$$

e. SEIR model

In this model we find a new class of individual, the exposed class (E). In this class the individual is in an incubation period. In other words, they have no symptoms and are unable to infect other people (Figure 3.1-4).

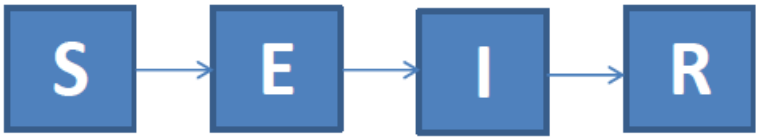


Figure 3.1-4 SEIR model flowchart. Susceptible- Exposed- Infected-Recovered (María González et al., 2017).

The model is described according to the following equations, where B is the number of births per unit of time, β is the rate of infection, μ is the average rate of deaths from natural causes, γ is the incubation rate and ϵ is the average time of infection.

$$\frac{dS}{dt} = B - \beta * S * I + \mu S \qquad (3.12)$$

$$\frac{dE}{dt} = \beta * S * I - (\epsilon + \mu) * E \qquad (3.13)$$

$$\frac{dI}{dt} = \epsilon * E - (\gamma + \mu) * I \qquad (3.14)$$

$$\frac{dR}{dt} = \gamma * I - \mu * R \qquad (3.15)$$

3.2 Mathematical models for HIV

In order to study the natural history of HIV we can use compartmental models but instead of using individuals with a different infectious state, we use a compartmental model that refers to the type of cells.

The primary purpose of a mathematical model on HIV transmission is to plan results at the population level from an individual level-analysis. There are several possibilities to study a model. For example, we can study it from the incidence of infection, the prevalence of infection, or the time of duplication of the epidemic, although the simplest way is to calculate the probability of an epidemic occurring. In epidemiology, this result is obtained from a simple summary statistic: the reproduction number of the infectious process, R_0. In a susceptible population, R_0 represents the expected number of secondary infections generated by the first infected individual. If R_0 is 1 or

higher, an epidemic is expected, instead with an R_0 less than 1 the infection is expected to disappear.

R_0 is a function of biological and behavioral factors. For a simple homogeneous population, it is defined as:

$$R_0 = \beta c D \qquad (3.16)$$

Where the terms that make up the equation are the average probability of sexual contact transmission (β), the average number of sexual partners formed per unit of time (c), and the average infectious duration of an infected individual (D).

All mathematical models divide the population into states and define the process and speed of movement between these states. Deterministic models are generally based on groupings or macro-level states, while stochastic models are used at a more individual level. The main difference between deterministic and stochastic models is how they define the movement between states. Deterministic models define dynamics using the average transition rate between states. Stochastic models, however, define dynamics using the probability that an individual will transition from one state to another.

Then, we can observe some factors that we must consider in order to study the parameters described in the equation.

a. <u>Probability of Sexual Contact Transmission (β)</u>

This parameter represents two components of transmission: the infectivity of the HIV-positive partner and the susceptibility of the HIV-negative partner (Cassels, Clark and Morris, 2008). Both components may depend on demographic, behavioral and biological factors.

- Demographic heterogeneity

The probability of transmission through heterosexual sex is higher from male to female. On the other hand, high rates of infection among young women in many sub-Saharan African countries led to theories that susceptibility may vary with age.

- Stage of the condition

There is compelling evidence that with people infected with HIV, ineffectiveness is not constant over time, but varies depending on the stage of infection and viral load. Most studies agree that the

likelihood of transmission of the infection peaks in the acute phase, decreases during the latent phase and then increases during the symptomatic stage.

- Co-infection with other STDs

Co-infection with HIV and other pathogens is thought to have strong implications for ineffectiveness and susceptibility. For example, herpes simplex virus type 2 (HSV-2) is associated with a 2 to 4 times higher risk of getting HIV-1.

- Circumcision

Male circumcision has recently been shown to reduce annual susceptibility to HIV infection by approximately 60%.

b. Contact rate (c)

This parameter denotes the average rate of change of sexual partner, or the contact rate.

- Central group theory

Studies of patients with sexually transmitted diseases in the United States in the late 1970s found that between 3% and 7% of infected people accounted for approximately 30% of the case load. These were people with high contact rates who would quickly re-infect thereafter after treatment.

- Selective mixing

Early studies assumed that members of the central group selected their partners at random, but the researchers realized that this assumption could be erroneous. Mathematical models introduced selective mixing and showed that the degree of mixing between the groups had a great influence on the pattern and spread of sexually transmitted diseases and HIV. We can define selective mixing by the variability between male or female partners. In general, selective mixing by activity level was shown to lead to faster but restricted propagation, while messy mixing leads to slower but more penetrating propagation.

- Social influences on behavior

The social context can also influence individual behavior and contact rate, and therefore HIV outcomes at the population level.

c. Duration of infection

The HIV condition is defined by at least 3 stages that coincide with viral load and CD_4 cell count: acute infection, asymptomatic stage, and symptomatic stage. The main focus of models examining

the impact of duration is the role of antiretrovirals. ART reduces viral load and the likelihood of transmission. Although it also reduces mortality and increases life expectancy.

3.2.1 Review of mathematical models of HIV

Some previous studies on the modelling of HIV disease are set out in this section. Cases are distributed depending on whether or not they perform any treatment and the type of model studied, as well as whether the infection is HIV or AIDS. In Tables 3.2-1, 3.2-2, 3.2-3, 3.2-4, 3.2-5 and 3.2-6 we find different articles that represent a model of the natural history of HIV. On the other hand, the epidemiological models are represented in Table 3.2-7.

Table 3.2-1 Mathematical model natural history of HIV including treatment. Representation of susceptible cells, infected cells and the virus (Hill, 2018).

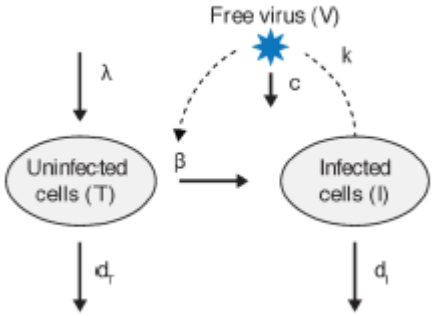
Type of model	Elements considered	HIV/AIDS	Treatment	Diagram	Equations	Reference
Basic viral dynamics model	T: Uninfected target cells I: Infected cells V: Free virus	HIV	No		$T=\lambda-\beta TV-d_T T$ $I=\beta TV-d_I I$ $V=kI-cV$	A. L. Hill (2008), "Mathematical Models of HIV Latency," in *Current Topics in Microbiology and Immunology*, vol. 417, Springer Verlag, 131–156.

Table 3.2-2 Mathematical model clinical course of HIV. Representation of susceptible cells, infected cells and the virus (Hill, 2018).

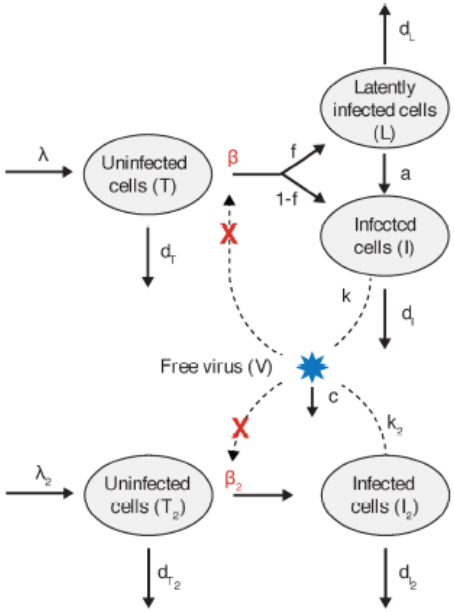
Type of model	Elements considered	HIV/AIDS	Treatment	Diagram	Equations	Reference
HIV dynamics under antiretroviral therapy	T: Uninfected target cells T_2: Uninfected target cells I: Infected cells I_2: Infected cells V: Free virus L: latently infected cells	HIV	Yes		$T=\lambda-\beta TV-d_T T$ $T_2=\lambda_2-\beta_2 T_2 V-d_{T2} T_2$ $I=(1-f)\beta TV-d_I I+aL$ $L=f\beta TV-d_L L-aL$ $I_2=\beta_2 T_2 V-d_{I2} I_2$ $V=kI+k_2 I_2-cV$	A. L. Hill (2018), "Mathematical Models of HIV Latency," in *Current Topics in Microbiology and Immunology*, vol. 417, Springer Verlag, 131–156.

Table 3.2-3 Mathematical model natural history of HIV. Representation of susceptible cells, infected cells and the virus (Alizon and Magnus, 2012).

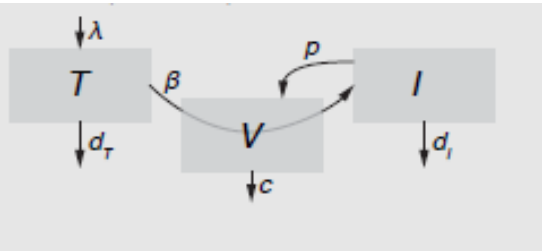
Type of model	Elements considered	HIV/AIDS	Treatment	Diagram	Equations	Reference
Basic viral dynamics model	T: Uninfected target cells I: Infected cells V: Free virus	HIV	No		$T=\lambda - d_T T - \beta VT$ $I=\beta TV - d_I I$ $V=pI - cV$	S. Alizon and C. Magnus (2012), "Modelling the course of an HIV infection: Insights from ecology and evolution," *Viruses*, vol. 4, no. 10. Multidisciplinary Digital Publishing Institute (MDPI), 1984–2013.

Table 3.2-4 Mathematical models natural history of HIV. Representation of susceptible cells, infected cells and the virus (Wodarz, 2008).

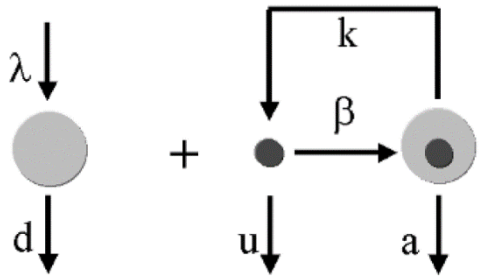
Type of model	Elements considered	HIV/AIDS	Treatment	Diagram	Equations	Reference
Basic viral dynamics model	X:Uninfected target cells Y: Infected cells V: Free virus	HIV	No		x= λ-dx-βxv y=βxv-ay v=ky-uv	D. Wodarz (2008), "Mathematical models of HIV and the immune system,"193–215.

Table 3.2-5 Mathematical models natural history and clinical course of HIV. Representation of susceptible cells, infected cells and the virus (Perelson, 2002).

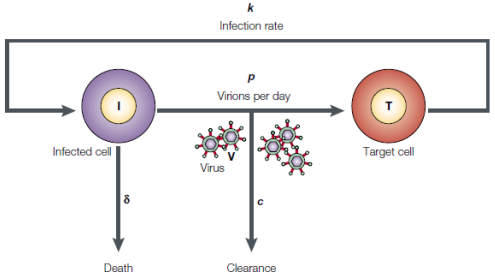
Type of model	Elements considered	HIV/AIDS	Treatment	Diagram	Equations	Reference
Basic viral dynamics model	T: Uninfected target cells I: Infected cells V: Infectious virus	HIV	No		$dT/dt= \lambda-dT-kVT$ $dI/dt=kVT-\delta I$ $dV/dt=pI-cV$	A. S. Perelson (2002), "Modelling viral and immune system dynamics," *Nature Reviews Immunology*, vol. 2, no. 1. European Association for Cardio-Thoracic Surgery, 28–36.
HIV dynamics under antiretroviral therapy	T: Uninfected target cells I: Infected cells V_I: Infectious virus V_{NI}: Non infectious virus	HIV	Yes		$dT/dt= \lambda-dT-(1-\varepsilon_{RT})kV_IT$ $dI/dt=(1-\varepsilon_{RT})kV_IT)-\delta I$ $dV_I/dt=(1-\varepsilon_{PI})pI-cV_I$ $dV_{NI}/dt= \varepsilon_{PI}pI-cV_{NI}$	A. S. Perelson (2002), "Modelling viral and immune system dynamics," *Nature Reviews Immunology*, vol. 2, no. 1. European Association for Cardio-Thoracic Surgery, 28–36.

Table 3.2-6 Mathematical models natural history and clinical course of HIV. Representation of susceptible cells, infected cells and the virus (Ribeiro and Perelson, 2004).

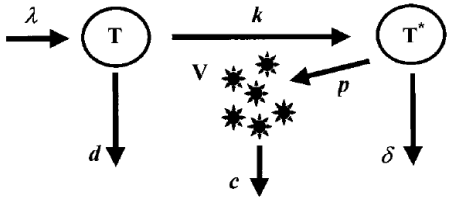
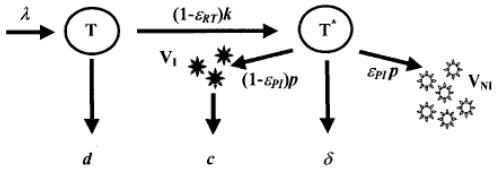
Type of model	Elements considered	HIV/AIDS	Treatment	Diagram	Equations	Reference
Basic viral dynamics model	T:Uninfected target cells T*: Infected cells V: Infectious virus	HIV	No		dT/dt= λ-dT-kVT dT*/dt=kVT-δT* dV/dt=pT*-cV	R. M. Ribeiro and A. S. Perelson, "The Analysis of HIV Dynamics Using Mathematical Models," 2004
HIV dynamics under antiretroviral therapy	T:Uninfected target cells T*: Infected cells V_I: Infectious virus V_{NI}: Non infectious virus	HIV	Yes		$dT/dt= \lambda-dT-(1-\varepsilon_{RT})kV_IT$ $dT^*/dt=(1-\varepsilon_{RT})kV_IT- \delta T^*$ $dV_I/dt=(1-\varepsilon_{PI})pT^*-cV_I$ $dV_{NI}/dt= \varepsilon_{PI}pT^*-cV_{NI}$	R. M. Ribeiro and A. S. Perelson, "The Analysis of HIV Dynamics Using Mathematical Models," 2004

Table 3.2-7 HIV epidemiological models (May and Anderson, 1987; Low-Beer and Stoneburner, 1997).

Elements considered	HIV/AIDS	Equations	Reference
HIV prevalence Country demographic data Profile of the sexual risk of HIV infection by age	HIV	$A_{t+n} = I_t \cdot \exp[-yn^c]$ $S_a = S_p\left(1+\left[\left(a-a_2\right)/\left(a_2-a_1\right)\right]\right)^{m_1} \times\left(1-\left[\left(a-a_2\right)/\left(a_3-a_2\right)\right]\right)^{m_2}$	D. Low-Beer and R. L. Stoneburner, "An age- and sex-structured HIV epidemiological model: features and applications.," *Bull. World Health Organ.*, vol. 75, no. 3, pp. 213–21, 1997.
Distributed incubation periods Heterogeneity in sexual activity Mortality	HIV	$H(t) = yv^{-y}t\exp[-(t/y)^v]$ $R_0' = (\beta_1\beta_2 c_1 c_2)^{1/2} D$ $R_0 = fR_{01} + (1-f)R_{02}$	R. M. May and R. M. Anderson, "Transmission dynamics of HIV infection," *Nature*, vol. 326, no. 6109, pp. 137–142, 1987, doi: 10.1038/326137a0.

The tables obtained in point 3.2.1 have been carried out by searching for information in different scientific articles at the web of science. As we can see from table 3.2-1 to 3.2-6, they all have in common the study of the natural history and clinical course of HIV. They show us the evolution of healthy cells, infected cells and the virus as the time goes on. As part of natural history, we understand that the course of events that occur in the human organism are as follows – from initial infection, to development of the disease, and subsequently its final outcome. In general, this outcome would be healing, chronic presence of the illness, or death. The difference between natural history and the clinical course is that in the natural history of a disease evolution is studied without medical intervention. When the human being receives treatment, it is considered a clinical course.

On the other hand, in Table 3.2.4, we have some models that study the epidemiology of the virus. In this case we refer to the study of the distribution and determinants of states or events related to health and the application of these studies to disease control and other health problems. These

take into account mortality, geographical distribution and the risk of contracting infection according to age. Some of these models have been implemented in the Matlab program, in which you can study the graphic evolution of these equations, as well as the parameters used for each case.

3.3 Implementation of models in Matlab

3.3.1 The basic viral dynamics model

With the data obtained in the article (Hill, 2018), the basic viral model of HIV has been implemented, which shows the evolution of viral load as well as uninfected cells. The resolution of the equations has been carried out thanks to the ode15s tool. Once the program has been implemented, we have obtained the figures (3.3-1 and 3.3-3), which we compare with those obtained in the article (Figure 3.3-2 and 3.3-4).

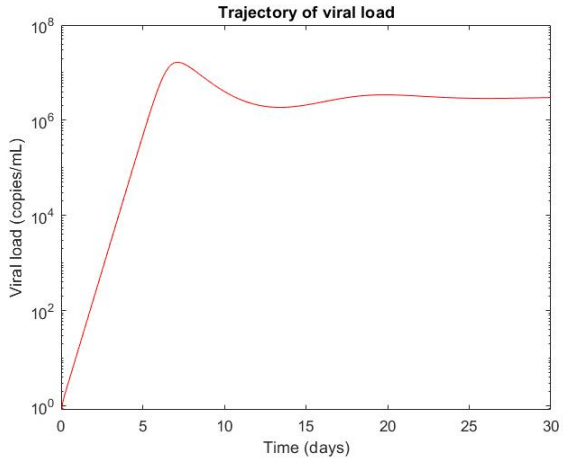


Figure 3.3-2 Matlab model graphic. It shows you the amount of viral load that the body has as the time goes by.

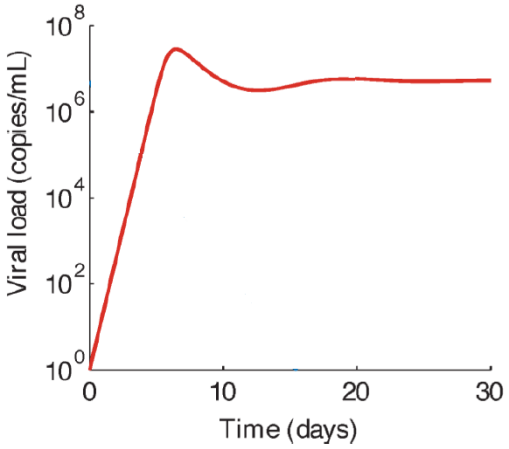


Figure 3.3-1 Article model. It shows you the amount of viral load that the body has as the time goes by. (Hill, 2018)

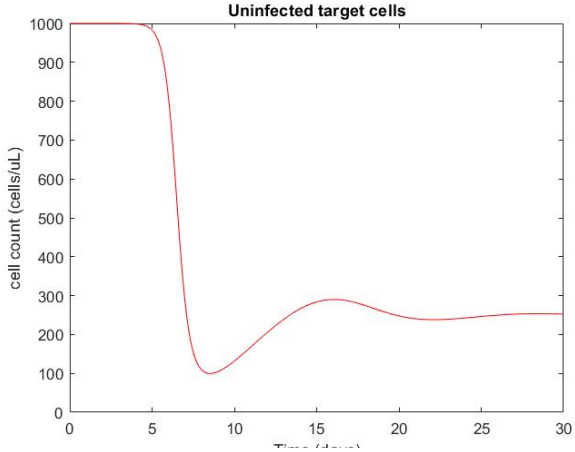


Figure 3.3-3 Matlab model. Number of uninfected cells as the time goes by.

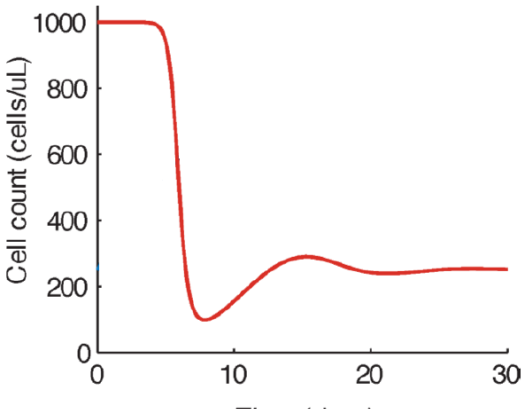


Figure 3.3-4 Article model. Number of uninfected cells as the time goes by (Hill, 2018).

Once the graphs have been obtained using the Matlab program, we can see that the results of the implementation match with those of the article.

As we can observe, in graphs 3.3-1 and 3.3-2, the first eight days the viral load is very high, this is due to the transition from healthy person to HIV-infected. After this, the viral load decreases and stays constant. On the other hand, we can see that both graphs 3.3-1 and 3.3-3are related between them, the fewer CD_4 cells infected, the viral load is also lower. This may be because the virus does not generate many copies of ARNs and is in a silent period. These graphs fit the stage of acute HIV infection.

3.3.2 HIV under antiretroviral therapy

With the data obtained in the article (Hill, 2018), a program has been implemented in Matlab on the evolution of infected cells and viral load under the effect of antiretroviral therapy. The resolution of the equations has been carried out by the Euler method of finite differences. Once the program has been implemented, we have obtained the figures (3.3-5 and 3.3-7) which we compare with those obtained in the article (Figures 3.3-6 and 3.3-8).

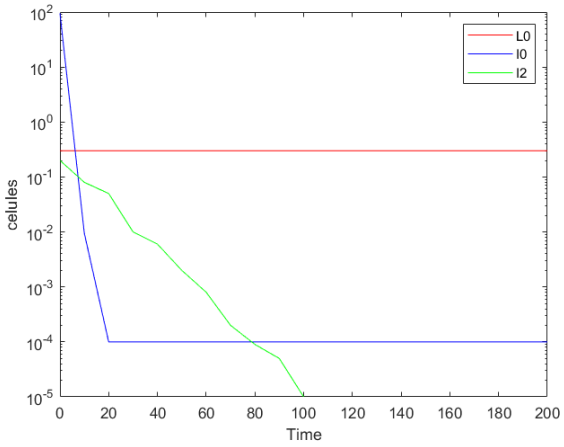


Figure 3.3-5 Matlab model. Evolution of the infected cells as time goes by In red we have the cells in a latent state, in blue the active cells and in green another type of infected cells.

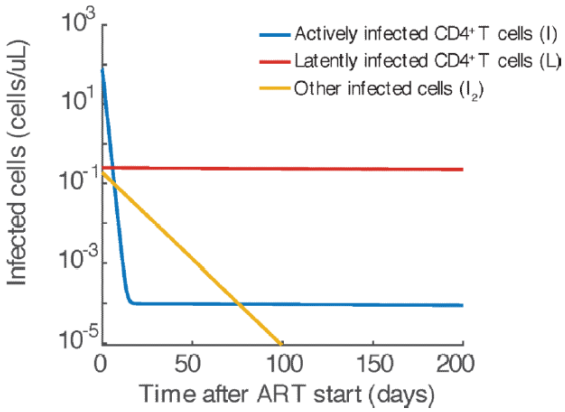


Figure 3.3-6 Article model. Evolution of the infected cells as time goes by In red we have the cells in a latent state, in blue the active cells and in green another type of infected cells (Hill, 2018).

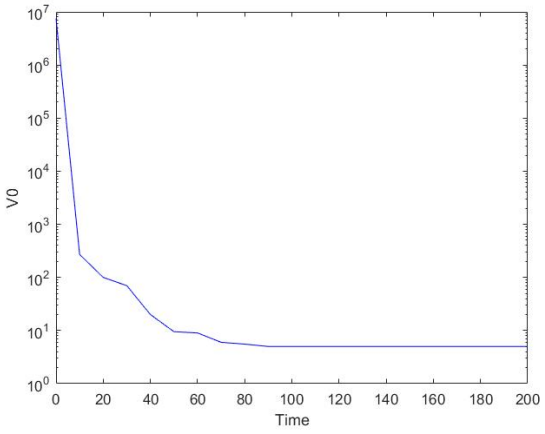


Figure 3.3-7 Matlab model and Excel values. This graph shows the evolution of viral load over time.

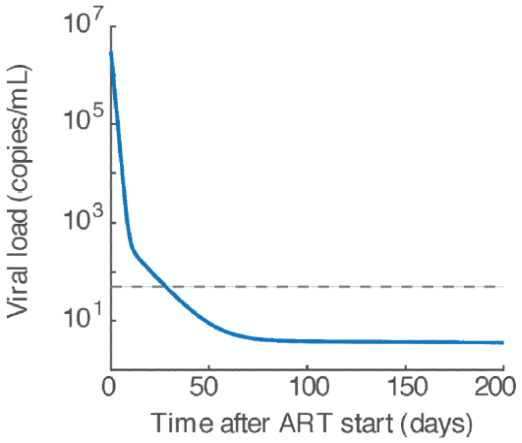


Figure 3.3-8 Article model. Evolution of viral load over time (Hill, 2018).

Once the graphs have been obtained using the Matlab program, we can see that the results of the implementation are very similiar with those of the article.

As we can observe in Figures 3.3-7 and 3.3-8, thanks to antiretroviral treatment, the viral load falls exponentially until it remains constant at very low values. Therefore, we can say that antiretroviral drugs are fast at preventing the virus from responding quickly. It should also be said that antiretroviral treatment does not have an immediate effect. In order to see the results of the medication, it must be taken over a long period of time.

With respect to graphs 3.3-5 and 3.3-6, latent cells are kept constant thanks to antiretroviral treatment. This helps the cells to become inactive and thus prevent them from infecting other healthy cells. On the other hand, active cells and other infected cells decrease until they are at very low values, this is because the drug does not allow latent cells to reproduce correctly and therefore, once the active cells die, there are no other cells that replace them.

4 Conclusions

In this work, a deep bibliographic review of HIV natural history and epidemiology has been carried out with a final implementation of different published mathematical models with the Matlab program. HIV infection still presents many unknowns for researchers today. There is no cure, but it is also not explained how two people have previously recovered from the virus. The first case was Timothy Ray Brown, who was cured of HIV in 2008 through treatment for leukemia and bone marrow transplants. The second case occurred in 2019 with a patient in London after also receiving a bone marrow transplant. Today none of these people have a trace of the virus in their body, so we can say that they have been completely cured.

The bibliographic review has been studied from the biological cycle of the virus and how its mechanisms work to obtain epidemiological data from it. Today, there are many drugs that allow us to block the reproduction of the virus, but none of them allow total recovery. That is why they are dealing with combinations of more tolerable and efficient remedies for the best treatment of comorbidities, HIV infection, sexually transmitted infections, and more. In addition, there are preventive methods such as pre-exposure prophylaxis, used by people at risk or more exposed to HIV, such as serodiscordant couples, gay men and sex workers.

Thanks to medical advances, HIV cases are decreasing every year, although there are exceptions in certain regions of the world, such as sub-Saharan Africa.

In relation to the mathematical models carried out, we can see that there is a great difference when antiretroviral therapy is administered. Where one model reflects the viral load in a population, the other reflects the number of infected cells. Overall, by applying these therapies we can hope to understand how we can continue to treat the virus among a wide number of individuals.

5 Prospects

The research presented in this bachelor thesis was mainly done in collaboration with the research group *Computational Biology and Complex Systems*.

We have reached the specific objectives of this initial phase but, in order to understand better the human immunodeficiency virus and improve the quality of life of humans, the research must go on.

After studying the epidemiology of HIV in the world, it has been seen that there are still many annual HIV infections. For this reason, the study of modelling is important to try to prevent the pandemic from spreading more than expected by studying its functionality and its capacity for transmission.

The development of this work has allowed me to better understand the importance of sexually transmitted diseases (STDs) such as HIV/AIDS. It is important to continue researching and to make people aware that it is a virus that affects many people in the world, and that does not take into account race, sex or social status. The awareness of the population, together with the study of resources, is indispensable to put an end to this pandemic, which takes many lives every year.

Bibliography

¿Cuáles Son Los Síntomas Del Vih/Sida? (No Date). Available At: Https://Www.Plannedparenthood.Org/Es/Temas-De-Salud/Enfermedades-De-Transmision-Sexual-Ets/Vih-Sida/Cuales-Son-Los-Sintomas-Del-Vihsida

¿Qué Es Una Infección Oportunista? | El Vih/Sida | Infosida (No Date). Available At: Https://Infosida.Nih.Gov/Understanding-Hiv-Aids/Fact-Sheets/26/86/-Que-Es-Una-Infeccion-Oportunista.

Alizon, S. And Magnus, C. (2012) 'Modelling The Course Of An Hiv Infection: Insights From Ecology And Evolution', *Viruses*. Multidisciplinary Digital Publishing Institute (Mdpi),1984–2013. Doi: 10.3390/V4101984.

Almeda, J. *Et Al.* (2002) 'Recomendaciones Para La Profilaxis Postexposición No Ocupacional Al Vih', *Enfermedades Infecciosas Y Microbiologia Clinica*. Elsevier, 20(8),391–400. Doi: 10.1016/S0213-005x(02)72826-7.

Álvarez, R.I. (2017). Interpretación De Las Pruebas Usadas Para Diagnosticar La Infección Por Virus De La Inmunodeficiencia Humana. Acta Médica Peruana, 34(4), 309-316. Http://Www.Scielo.Org.Pe/Scielo.Php?Script=Sci_Arttext&Pid=S172859172017000400009&Lng=Es&Tlng=Es

Analisis Consumo Drogas | Farmaceuticos | Historia Del Vih/Sida| (No Date). Available At: Http://Www.Tododrogas.Net/Otr/Sida/Index.Html

Antonio, J. And Castillo, L. (2004) *Infección-Enfermedad Por Vih/Sida*, *Medisan*.

Burke, L. A. And Gulick, R. M. (2018) 'Entry Inhibitors', In *Encyclopedia Of Aids*. Springer New York, 485–496. Doi: 10.1007/978-1-4939-7101-5_447.

Buttò, S. *Et Al.* (2010) 'Laboratory Diagnostics For Hiv Infection / Test Di Laboratorio Per La Diagnosi Di Infezione Da Hiv', *Annali Dell'istituto Superiore Di Sanità*, 46(1), 24–33. Doi: 10.4415/Ann_10_01_04.

Cassels, S., Clark, S. J. And Morris, M. (2008) 'Mathematical Models For Hiv Transmission Dynamics: Tools For Social And Behavioral Science Research', In *Journal Of Acquired Immune Deficiency Syndromes*. Nih Public Access, S34. Doi: 10.1097/Qai.0b013e3181605da3.

Castro, J. Et Al. (No Date) *Acta Med Per 24(3) 2007 208 Artículos De Revisión: Actualización Para El Médico No Especialista En El Tratamiento Del Vih*.

Cayetana Fdez-Setién Fdez, M. (No Date) *El Vih/Sida Y Los Actuales Métodos Profilácticos*.

Chen, A. And Dowdy, D. W. (2014) 'Clinical Effectiveness And Cost-Effectiveness Of Hiv Pre-Exposure Prophylaxis In Men Who Have Sex With Men: Risk Calculators For Real-World Decision-Making', *Plos One*, 9(10) Doi: 10.1371/Journal.Pone.0108742.

Chung, J., Rossi, J. J. And Jung, U. (2011) 'Current Progress And Challenges In Hiv Gene Therapy', *Future Virology*, 1319–1328. Doi: 10.2217/Fvl.11.113.

Cordeiro, N. And Taroco, R. (No Date) *Temas De Bacteriología Y Virología Médica Retrovirus Y Vih*.

López, S., Garrido, F., Hernández, M. (2000) Desarrollo Histórico De La Epidemiología: Su Formación Como Disciplina Científica. Salud Pública De México, [S.L.], V. 42, N. 2, 133-143 Http://Saludpublica.Mx/Index.Php/Spm/Article/View/6221/7399

Farzadegan, H. *Et Al.* (1998) 'Sex Differences In Hiv-1 Viral Load And Progression To Aids', *Lancet*. Elsevier Limited, 352(9139), 1510–1514. Doi: 10.1016/S0140-6736(98)02372-1.

Ferrández, J. S. R. And Sesmero, J. M. M. (2016) 'Pre-Exposure Prophylaxis For The Prevention Of Hiv Infection: A New Prevention Paradigm?', *Farmacia Hospitalaria*. Sociedad Espanola De Farmacia Hospitalaria, 40(3), 219–224. Doi: 10.7399/Fh.2016.40.3.10439.

García, F. *Et Al.* (2011) 'Diagnóstico De Laboratorio De La Infección Por El Vih, Del Tropismo Viral Y De Las Resistencias A Los Antirretrovirales', *Enfermedades Infecciosas Y Microbiologia Clinica*, 29(4), 297–307. Doi: 10.1016/J.Eimc.2010.12.006.

Gómez,M., Nápoles, M.. (2009). Historia Y Teorías De La Aparición Del Virus De La Inmunodeficiencia Humana. Revista Cubana De Medicina Militar, 38(3-4) Http://Scielo.Sld.Cu/Scielo.Php?Script=Sci_Arttext&Pid=S013865572009000300007&Lng=Es&Tlng=Es

Haefner, J. W. (2005). Modeling Biological Systems: Principles And Applications. Springer Science & Business Media. Retrieved From Https://Books.Google.Com/Books?Id=Teuefw0qhj4c&Pgis=1

Hill, A. L. (2018) 'Mathematical Models Of Hiv Latency', In *Current Topics In Microbiology And Immunology*. Springer Verlag, 131–156. Doi: 10.1007/82_2017_77.

Hiv Progression | Definition | Aidsinfo (No Date). Available At: Https://Aidsinfo.Nih.Gov/Understanding-Hiv-Aids/Glossary/3387/Hiv-Progression

Hoja Informativa-Dia Mundial Del Sida 2019.

Kirchhoff, F. *Et Al.* (1995) 'Absence Of Intact Nef Sequences In A Long-Term Survivor With Nonprogressive Hiv-1 Infection', *New England Journal Of Medicine*. Massachusetts Medical Society , 332(4), 228–232. Doi: 10.1056/Nejm199501263320405.

Lamotte, J.A. (2014). Infección Por Vih/Sida En El Mundo Actual. Medisan, 18(7), 993-1013. Http://Scielo.Sld.Cu/Scielo.Php?Script=Sci_Arttext&Pid=S102930192014000700015&Lng=Es&Tlng=Es.

Low-Beer, D. And Stoneburner, R. L. (1997) 'An Age- And Sex-Structured Hiv Epidemiological Model: Features And Applications.', *Bulletin Of The World Health Organization*. World Health Organization, 75(3),213–21. Available At: Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/9277008

Lozano, F. And Domingo, P. (2011) 'Antiretroviral Therapy For Hiv Infection', *Enfermedades Infecciosas Y Microbiologia Clinica*. Elsevier Doyma, 29(6), 455–465. Doi: 10.1016/J.Eimc.2011.02.009.

María González, P. *Et Al.* (2017) *Modelización Y Simulación En Epidemiología*.

May, R. M. And Anderson, R. M. (1987) 'Transmission Dynamics Of Hiv Infection', *Nature*. Nature Publishing Group, 326(6109), 137–142. Doi: 10.1038/326137a0.

Mecanicismo | Diccionario De La Lengua Española | Rae - Asale (No Date). Available At: Https://Dle.Rae.Es/Mecanicismo.

Meditz, A., Mawhinney, S., Et Al. (2011). Sex, Race, And Geographic Region Influence Clinical Outcomes Following Primary Hiv-1 Infection. The Journal Of Infectious Diseases. 203. 442-51. 10.1093/Infdis/Jiq085.

Nacional Sobre Sida Grupo De Expertos Prep, P. El (2018) *Documento De Consenso - Profilaxis Preexposición Al Vih En España*.

Perelson, A. S. (2002) 'Modelling Viral And Immune System Dynamics', *Nature Reviews Immunology*. European Association For Cardio-Thoracic Surgery, 28–36. Doi: 10.1038/Nri700.

Pinkerton, S. D. *Et Al.* (2004) 'Cost-Effectiveness Of Postexposure Prophylaxis After Sexual Or Injection-Drug Exposure To Human Immunodeficiency Virus', *Archives Of Internal Medicine*, 164(1), 46–54. Doi: 10.1001/Archinte.164.1.46.

Pradas, F. (No Date) *Diseño Y Tipos De Estudios Epidemiológicos*.

Probabilidades De Contraer El Vih | Consultorio Todosida ¡Acción De Prevención Contra El Vih/Sida/Its! (No Date). Available At: Http://Www.Todosida.Org/Probabilidades-Contraer-Vih.

Profilaxis Posexposición (Pep) | Definición | Infosida (No Date). Available At: Https://Infosida.Nih.Gov/Understanding-Hiv-Aids/Glossary/3973/Profilaxis-Posexposicion.

Pruebas De Detección Del Vih | El Vih/Sida | Infosida (No Date). Available At: Https://Infosida.Nih.Gov/Understanding-Hiv-Aids/Fact-Sheets/19/47/Pruebas-De-Deteccion-Del-Vih.

Relación Con Vih, E. El And Vhc En Adultos Y Niños, V. Y. (No Date) *Documento De Consenso Sobre Profilaxis Postexposición Ocupacional Y No Ocupacional*.

Ribeiro, R. M. And Perelson, A. S. (2004) *The Analysis Of Hiv Dynamics Using Mathematical Models*.

Rockstroh Jk, L. J. D. E. Et Al (2011) *Long-Term Treatment With Raltegravir Or Efavirenz Combined With Tenofovir/Emtricitabine For Treatment-Naive Human Immunodeficiency Virus-1-Infected... - Pubmed - Ncbi*. Available At: Https://Www.Ncbi.Nlm.Nih.Gov/Pubmed/21921224.

Rosas, A. Et Al. (2013) 'Características Estructurales Y Funcionales Del Vih'.

Rubio, R *Et Al.* (2010) *Tratamiento De La Infección Por El Vih. Fármacos Antirretrovirales*, *Medicine*. Doi: 10.1016/S0304-5412(10)70160-8.

Rubio, R. *Et Al.* (2010) 'Treatment Of Hiv Infection. Antiretroviral Drugs', *Medicine*. Ediciones Doyma, S.L., 10(59), 4048–4060. Doi: 10.1016/S0304-5412(10)70160-8.

Sharp, P. M. And Hahn, B. H. (2011) 'Origins Of Hiv And The Aids Pandemic', *Cold Spring Harbor Perspectives In Medicine*. Cold Spring Harbor Laboratory Press, 1(1). Doi: 10.1101/Cshperspect.A006841.

De Sistemas, M., Introducción, B. And Modelización, S. Y. (No Date) *Modelización De Sistemas Biológicos*.

Tanuma, J. *Et Al.* (2017) 'Long-Term Viral Suppression And Immune Recovery During First-Line Antiretroviral Therapy: A Study Of An Hiv-Infected Adult Cohort In Hanoi, Vietnam: A', *Journal Of The International Aids Society*. Wiley Blackwell, 20(4), Doi: 10.1002/Jia2.25030.

The Stages Of Hiv Infection | Understanding Hiv/Aids | Aidsinfo (No Date). Available At: Https://Aidsinfo.Nih.Gov/Understanding-Hiv-Aids/Fact-Sheets/19/46/The-Stages-Of-Hiv-Infection.

Transmisión Del Vih | Información Básica | Vih/Sida | Cdc (No Date). Available At: Https://Www.Cdc.Gov/Hiv/Spanish/Basics/Transmission.Html.

Unaids (2019) *Unaids Data 2019*.

Vigilància Epidemiològica De La Infecció Pel Vih I La Sida A Catalunya (2019). Available At: Www.Ceeiscat.Cat.

Vigilancia Epidemiológica Del Vih Y Sida En España 2018 Sistema De Información Sobre Nuevos Diagnósticos De Vih Registro Nacional De Casos De Sida Dirección General De Salud Pública, Calidad E Innovación Sistemas Autonómicos De Vigilancia Epidemiológica (2019).

Vih/Sida: Conceptos Básicos | El Vih/Sida | Infosida (No Date). Available At: Https://Infosida.Nih.Gov/Understanding-Hiv-Aids/Fact-Sheets/19/45/Vih-Sida--Conceptos-Basicos.

Walmsley, S. L. *Et Al.* (2013) 'Dolutegravir Plus Abacavir-Lamivudine For The Treatment Of Hiv-1 Infection', *New England Journal Of Medicine*. Massachussetts Medical Society, 369(19), 1807–1818. Doi: 10.1056/Nejmoa1215541.

What Are Hiv And Aids? | Hiv.Gov (No Date). Available At: Https://Www.Hiv.Gov/Hiv-Basics/Overview/About-Hiv-And-Aids/What-Are-Hiv-And-Aids.

Wodarz, D. (2008) 'Mathematical Models Of Hiv And The Immune System', 193–215.

Ziegler, S. And Altfeld, M. (2016) 'Sex Differences In Hiv-1-Mediated Immunopathology', *Current Opinion In Hiv And Aids*. Lippincott Williams And Wilkins, 209–215. Doi: 10.1097/Coh.0000000000000237.

Annex: HIV drugs

- Reverse transcriptase inhibitors analogous to nucleosides and nucleotides (ITINs)

Table 3.3-1 Nucleoside and nucleotide-analog reverse transcriptase inhibitors (R Rubio *et al.*, 2010)

Generic name	**Zidovudine ZDV**	**Didanosine ddI**	**Stavudine d4T**	**Lamivudine 3TC**	**Emtricitabine FTC**	**Abacavir ABC**	**Tenofovir TDF**
Trade name	Retrovir Combivir Trizivir	Videx	Zerit	Epivir Combivir Trizivir Kivexa	Emtriva Truvada Atripla	Ziagen Trizivir Kivexa	Viread Truvada Atripla
Recommended dose	250-300 mg BID	< 60 kg: 250 mg QD o 125 mg BID >60kg: 400 mg QD o 200 mg BID	<60 kg: 30 mg BID >60 kg: 40 mg BID	150 mg BID 300 mg QD	200 mg QD	300 mg BID	300 mg QD
Activity	VIH-1,2	VIH-1,2	VIH-1,2	VIH-1,2 VHB	VIH-1,2 VHB	VIH-1,2	VIH-1,2 VHB
Adverse effects	Myelosuppression: anemia and/or neutropenia at high doses Headache Dizziness Gastrointestinal intolerance Lipodystrophy Lactic acidosis with hepatic steatosis	Pancreatitis Hyperuricemia Peripheral Neuropathy Diarrhea Nausea Lipodystrophy Lactic Acidosis with Hepatic Steatosis	Peropheric neuropathy Pancreatitis Lipodystrophy Lactic acidosis with hepatic steatosis	Digestive intolerance Headache Fatigue Abdominal pain Lipodystrophy Lactic acidosis with hepatic steatosis	Digestive intolerance Headache Skin Exanthema Elevation CPK Anemia/neutropenia Lipodystrophy Lactic Acidosis with Hepatic Steatosis	Hypersensitivity (5-8%) Lipodystrophy Lactic acidosis with hepatic steatosis	Digestive intolerance Headache Fatigue Abdominal Pain Proteinuria

- Non-nucleoside reverse transcriptase inhibitors (ITINN)

These drugs inhibit IT by joining with the enzyme regions outside the active place and causing changes in the enzyme formation that inactivate it. They do not need to be metabolized to be active.

Table 3.3-2 Non-nucleoside reverse transcriptase inhibitors (R Rubio *et al.*, 2010)

Generic name	**Nevirapine (NVP)**	**Efavirenz (EFV)**	**Etravirine (ETR)**
Trade name	Viramune	Sustiva Artipla	Intelence
Recommended dose	200 mg QD x 14 days followed by 200 mg BID	600 mg QD	200 mg BID
Activity	VIH-1	VIH-1	VIH-1
Adverse effects	Exanthema Increased Transaminases Acute Hepatitis	Exanthema Neuropsychiatric symptoms Increased transaminases Teratogenicity in monkeys	Exanthema Nauseas Diarrhea

- Protease inhibitors (IP)

Table 3.3-3 Protease Inhibitors. (R Rubio *et al.*, 2010)

Generic name	**Liponavir/ ritonavir**	**Atazanavir**	**Darunavir/ ritonavir**	**Tipranavir/ ritonavir**
Trade name	Kaletra	Reyataz	Prezista	Aptivus
Dose	400/100 mg every 12 hours	300/100 mg every 24 h or 400 mg every 24 h	600/100 mg every 12 hours (in pretreated patients) 800/100 QD (in patients without prior treatment	TPV/r 500/200 mg every 12 hours
Activity	VIH-1,2	VIH-1	VIH-1,2	VIH-1,2
Side effects	Intolerance G-I (vomiting, diarrhea) Headache Asthenia Hyperglycemia Dyslipidemia Lipodystrophy Possible increased bleeding in hemophiliacs	Hyperbilirubinemia GI intolerance (diarrhea) Headache Studies available at 48 weeks show no relevant lipid alterations ATV/r: mild dyslipidemia Possible increase in bleeding in hemophiliacs	Intolerance G-I (vomiting, diarrhea) Headache Asthenia Dyslipidemia Mild rash, which is usually moderate and self-limiting Possible increase in bleeding in hemophiliacs	Intolerance G-I (diarrhea) CNS disorders (vertigo, difficulty concentrating, slowing, mood swings) In combination with RTV, increased triglycerides and transaminases 14 cases of intracranial bleeding have been reported, 8 of which were fatal

Table 3.3-4 Protease II inhibitors. (R Rubio *et al.*, 2010)

Generic name	**Indinavir**	**Ritonavir**	**Saquinavir**	**Nelfinavir**	**Fosamprenavir**
Trade name	Crixivan	Norvir	Invirase	Viracept	Telzir
Dose	800 mg TID IDV/r 800/100 BID	As an enhancer of other IPs: 100 or 200 mg with each dose of IP As IP (600 mg IDB) is discouraged	SQV/r 1000/100 BID	750 mg TID 1250 mg BID	FPV/r 700/100 mg every 12 hours With or without food
Activity	VIH- 1,2	VIH- 1,2	VIH- 1,2	VIH- 1,2	VIH- 1,2
Side effects	Nephrolithiasis Intolerance G-I Hyperbilirubinemia Hyperglycemia Dyslipidemia Lipodystrophy Possible increase bleeding in hemophiliacs	(In reduced doses the prevalence of side effects is very low) Intolerance G-I Vomiting, diarrhea Oral paresthesia's Hepatitis Hyperglycemia Dyslipidemia Lipodystrophy Possible increase bleeding in hemophiliacs	Intolerance G-I Diarrhea Headache High transaminases Hyperglycemia Dyslipidemia Lipodystrophy Possible increase bleeding in hemophiliacs	Diarrhea Hyperglycemia Dyslipidemia Lipodystrophy Possible increase in bleeding in hemophiliacs	Intolerance G-I Diarrhea Exanthema Headache Hyperglycemia Dyslipidemia Lipodystrophy Possible increased bleeding in hemophiliacs

Annex: Matlab scripts

Basic viral dynamics model

Script main VIH

```
clear all
close all

% Initial conditions for X(1), X(2)...

X(1)=1000000; % susceptible cells
X(2)=0.03; % infectious cells
X(3)=0; % infectious virus
X(4)=1000; % Initial poblation
X(5)=300;
X(6)=4*10^6;


% tspan definition

tspan=(0:0.0467:30);

% Crida de ode15s
[T,Y] = ode15s(@ode_vih,tspan,X);


% Graphic output
figure
    plot(T(:),Y(:,4),'r')


    title('Trajectory of viral load')
    xlabel('Time (days)')
    ylabel('Viral load (copies/mL)')
    hold off

figure
semilogy(T(:),Y(:,3),'r')

title('Uninfected target cells')
    xlabel('Time (days)')
    ylabel('cell count (cells/uL)')
    hold off
```

Script ode VIH

```
function dXdt=ode_vih(t,X)

% Equations parameters: alpha, beta
landa=100000;  % source of susceptible cells
beta=0.0000001; % infected cells
k=1000;
dT=0.1;
dI=1;
c=25;
```

```
% Equations list: dXdt(1), dXdt(2),...

dXdt(1)=landa-beta*X(1)*X(3)-dT*X(1);
dXdt(2)=beta*X(1)*X(3)-dI*X(2);
dXdt(3)= (k*X(2))-(c*X(3));
dXdt(4)= dXdt(1)/1000;
dXdt(5)=landa-dT*X(5);
dXdt(6)=((landa*beta*k)/(dT*dI*c))-X(6);



% Vector transposition dXdt: dXdt=dXdt'
dXdt=dXdt';
```

HIV dynamics under antiretroviral therapy

```
clear all
close all


%Valor dels parametres
landa=0.1;
beta=0;
k=1000;
dT=0.1;
dI=1;
c=25;
landa2=0.00001;
beta2=0;
k2=100;
dT2=0.01;
dI2=0.1;
f=10^-4;
a=4*10^-4;
dL=10^-4;
t0=0;
tfin=200;
DeltaT=0.0416;

%Valor parametres inicials
T0=5000000;
T20=500;
I0=94.964;
L0=0.3;
I20=0.2;
V0=749998;

%Declaracions de variables
Temps = (t0:DeltaT:tfin);
Npunts=length(Temps);


%Valors inicials

T0(1)=T0;
T20(1)=T20;
I0(1)=I0;
```

```
L0(1)=L0;
I20(1)=I20;
V0(1)=V0;


for i=2:Npunts

   T0(i) = T0(i-1)+(landa - (beta*T0(i-1)*V0(i-1))-(dT*T0(i-
1)))*DeltaT;
   T20(i)= T20(i-1)+(landa2-beta2*T20(i-1)*V0(i-1)-dT2*T20(i-
1))*DeltaT;
   I0(i)= I0(i-1)+(((1-f)*beta*T0(i-1)*V0(i-1))-(dI*I0(i-1))+(a*L0(i-
1)))*DeltaT;
   L0(i)=L0(i-1)+(f*beta*T0(i-1)*V0(i-1)-dL*L0(i-1)-a*L0(i-1))*DeltaT;
   I20(i)=I20(i-1)+((beta2*T20(i-1)*V0(i-1))-(dI2*I20(i-1)))*DeltaT;
   V0(i)=V0(i-1)+(k*I0(i-1)+k2*I20(i-1)-c*V0(i-1))*DeltaT;


end

%Sortida gràfica
figure(1)
semilogy(Temps(:),V0(:),'b')
hold on
title ('Evolution of the viral load during a time')
xlabel('Time after ART start (days)')
ylabel('Viral load (copies/mL)')
hold off

figure(2)
semilogy(Temps(:),I0(:),'b')
    hold on
  semilogy (Temps(:),L0(:),'r')
    hold on
    semilogy (Temps(:),I20(:),'g')
    hold on
xlabel('Time after ART start (days)')
ylabel('Infected cells (cells/uL)')
legend('I0','L0','I20')
hold off
```

Adjusting the values: V0,I0,I2,L0

```
clear all
close all

%% Leemos los datos del Excel para V0

opts = spreadsheetImportOptions("NumVariables", 3);
opts.Sheet = "Hoja4";
opts.DataRange = "A2:C22";
opts.VariableNames = ["Tiempo4", "ValorV0Matlab",
"ValorV0Modelexperimental"];
opts.VariableTypes = ["double", "double", "double"];
tbl = readtable("Valores_matlab.xlsx", opts, "UseExcel", false);
Tiempo4 = tbl.Tiempo4;
ValorV0Matlab = tbl.ValorV0Matlab;
ValorV0Modelexperimental = tbl.ValorV0Modelexperimental;
```

```
clear opts tbl
%% Calculamos error y ploteamos

Diff=ValorV0Matlab-ValorV0Modelexperimental;
ErrorV0 = 1/(length(ValorV0Matlab))*sqrt(sum(Diff.^2));
ErrorV0

figure
semilogy(Tiempo4,ValorV0Matlab,'or-')
hold on
semilogy(Tiempo4, ValorV0Modelexperimental,'b')
xlabel('Time')
ylabel('V0')
legend('Model','Experimetal')
hold off

clear all
close all

%% Leemos los datos del Excel para L0

opts = spreadsheetImportOptions("NumVariables", 3);
opts.Sheet = "Hoja1";
opts.DataRange = "A2:C22";
opts.VariableNames = ["Tiempo1", "ValorL0Matlab",
"ValorL0Modelexperimental"];
opts.VariableTypes = ["double", "double", "double"];
tbl = readtable("Valores_matlab.xlsx", opts, "UseExcel", false);
Tiempo1 = tbl.Tiempo1;
ValorL0Matlab = tbl.ValorL0Matlab;
ValorL0Modelexperimental = tbl.ValorL0Modelexperimental;
clear opts tbl
%% Importamos Excel para I0
opts = spreadsheetImportOptions("NumVariables", 3);
opts.Sheet = "Hoja1";
opts.DataRange = "F2:H22";
opts.VariableNames = ["Tiempo2", "ValorI0Matlab",
"ValorI0Modelexperimental"];
opts.VariableTypes = ["double", "double", "double"];
tbl = readtable("Valores_matlab.xlsx", opts, "UseExcel", false);
Tiempo2 = tbl.Tiempo2;
ValorI0Matlab = tbl.ValorI0Matlab;
ValorI0Modelexperimental = tbl.ValorI0Modelexperimental;
clear opts tbl
 %% Importamos Excel para I2
opts = spreadsheetImportOptions("NumVariables", 3);
opts.Sheet = "Hoja1";
opts.DataRange = "K2:M12";
opts.VariableNames = ["Tiempo3", "ValorI2Matlab",
"ValorI2Modelexperimental"];
opts.VariableTypes = ["double", "double", "double"];
tbl = readtable("Valores_matlab.xlsx", opts, "UseExcel", false);
Tiempo3 = tbl.Tiempo3;
ValorI2Matlab = tbl.ValorI2Matlab;
ValorI2Modelexperimental = tbl.ValorI2Modelexperimental;
clear opts tbl
%% Calculamos error y ploteamos
Diff=ValorL0Matlab-ValorL0Modelexperimental;
ErrorL0 = 1/(length(ValorL0Matlab))*sqrt(sum(Diff.^2));
ErrorL0
Diff=ValorI2Matlab-ValorI2Modelexperimental;
```

```
ErrorI2 = 1/(length(ValorI2Matlab))*sqrt(sum(Diff.^2));
ErrorI2
Diff=ValorI0Matlab-ValorI0Modelexperimental;
ErrorI0 = 1/(length(ValorI0Matlab))*sqrt(sum(Diff.^2));
ErrorI0

figure
semilogy(Tiempo1, ValorL0Modelexperimental,'r')
hold on
semilogy(Tiempo2, ValorI0Modelexperimental,'b')
hold on
semilogy(Tiempo3,ValorI2Modelexperimental,'g')
xlabel('Time')
ylabel('celules')
legend('L0','I0','I2')
hold off
```