

Thirty-five years of HIV/AIDS in Chilean children and adolescents

Summary

The history of HIV/AIDS in Chilean children is described, from the detection of the first case in 1987 to date, with the main advances obtained by the Paediatric HIV/AIDS Care Programme, SOCHIPE/MINSAL. The follow-up and management of children and adolescents in this Program is described.

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Introduction

HIV/AIDS in the world

The first cases of HIV/AIDS were detected in the world in 1981 in adults and in 1982 and 1983 in children, by transfusion and mother-child respectively, and since then until the end of 2021, 84.2 million people had contracted the infection and 40.1 million had died from it. In 2021, 38.4 million people were living with HIV, 36.7 million over the age of 15 and 1.7 million children under the age of 15.¹ Globally, increased access to antiretroviral therapy (ART) has led to a large reduction in new infections and deaths. By 2021, 75% of all people living with HIV had access to ART: 76% of >15 years and 52% of <15 years. In the world there has been an increase in heterosexual transmission of HIV, and with it an increase in the number of infected women. In 2021, 54% of all people living with HIV were adult women and girls.¹ Almost women are infected with HIV through heterosexual transmission and at childbearing age, so there was initially an increase in HIV-exposed children/HIV-infected children, but thanks to the implementation of Vertical Transmission Prevention Protocols (VTPP) of HIV, infection in children has been reduced.²⁻⁵ By 2021, 80% of infected women over the age of 15 had access to ART and 81% of pregnant women received antiretrovirals (ARVs) to prevent HIV transmission to their children. From 2010 to 2021, infections in children decreased by 52% (1). Globally, 90 to 95% of children infected with HIV have been infected by vertical transmission (VT), which occurs most frequently in late pregnancy, intrapartum and peripartum (60-75%).⁶

HIV/AIDS in Chile

In Chile, the first cases of HIV/AIDS in adults were reported in 1984 in men and in 1985 in women. In children, the first cases were described in 1987 by transfusion and in 1989 by VT, mother-child.⁷⁻⁹ Thirty five years have passed since the detection of the first child infected with HIV in Chile. In Chile, unlike most other countries, there has been an increase in cases in the last 10 years, especially in adults.¹⁰⁻¹² As children are infected with HIV mainly through VT and thanks to the implementation of HIV VTPP in hospitals since 1995 and especially since 2005 with the promulgation by Minister of Health (Ministerio de Salud: MINSAL) of the first version of the HIV VT Prevention Norm, the number of children exposed to HIV and therefore the number of children infected with HIV has decreased, decrease that is seen especially in the age group of 0 to 9 years.¹³⁻¹⁶

From 1987 to June 2022, according to the figures from the Institute of Public Health (Instituto de Salud Pública: ISP), 486 children

infected with HIV have been detected [449 (92.4%) by VT, 37 (7.6%) by other causes], of them 256 (52.7%) women and 224 (46.1%) men.¹⁶

HIV/AIDS in Chilean children and adolescents

According to the 1994 classification of the US Center for Diseases Control and Prevention (CDC), HIV infection in children is that which occurs in children under 13 years of age.¹⁷

In 1990, the Infectious Diseases Branch of Chilean Society of Pediatrics (Sociedad Chilena de Pediatría: SOCHIPE), created the Paediatric HIV/AIDS Committee, which since 1992 has been working together with the Department of Sexually Transmitted Diseases (STI) and HIV/AIDS Programmes of MINSAL in the Paediatric HIV/AIDS Care Programme, with representatives currently from all regions of the country.⁹

The work of the Paediatric HIV/AIDS Care Programme has made a number of advances in the control of HIV-infected children and adolescents.

1987 to date: Improvement in the detection of children / adolescents infected with HIV.

HIV-infected children are screened either by detecting HIV-infected pregnant women, HIV-exposed newborns [children of HIV (+) mothers], or children already infected with HIV.

So far, most HIV-infected children have been detected in postnatal life by clinic manifestations. The diffusion of the topic throughout the country allowed an improvement in the survey with a decrease in the number of children detected by clinic manifestations from 47% in 2008 to 42% in 2014, a figure that remains until 2022 (43%), decrease in those detected in the AIDS stage from 41% in 2008 to 28% in 2014, and increase in those detected in the year of birth from 33% before 2005 (65 cases out of 196) to 50% from 2006 to 2014 (24 out of 49), and to 49% (55 out of 112) between 2015 and 2022.^{16,18-20} Many of the children detected after the year of their birth, were slow progressors who presented late manifestations.²¹ Until 2014, detection by maternal history was 35% and by admission to VTPP 10% (18-20). According to the latest statistics from the ISP, of the 486 infected children screened from 1987 to June of 2022, 100 (20.6%) were detected being under 3 months, 63 (13%) between 4 and 6 months of age, 114 (23.6%) between 7 months and one year, 209 (43%) between 2 and 12 years of age.¹⁶

So far, most of the children detected by clinical manifestations were for nonspecific manifestations (hepatomegaly, lymphadenopathy, splenomegaly, prolonged fever), respiratory, digestive, hematological,

nutritional, neurological, and infections by habitual agents of childhood and opportunistic agents (cytomegalovirus, candida, *Pneumocystis jirovecii*, *Cryptosporidium*, Herpes Simplex Virus, *Mycobacterium tuberculosis* and *Mycobacterium avium*. With the increased use of ART in children and with it improvement in survival, cancers began to be detected.^{18-20,22} As of 2008, 41 per cent of children had been detected in the AIDS stage and 59 per cent in non-AIDS stages. In 2014 these figures were 27.8% and 72% respectively (CDC Classification 1994).¹⁷⁻²⁰

Progress 1992-97: Lowering the age of confirmation or discarding of HIV infection with the application of the Polymerase Chain Reaction (PCR) technique.

When a newborn or a child HIV-exposed or a child/adolescent suspected of being infected with HIV is detected, a clinical and laboratory evaluation is performed with general, infectological, immunological (CD4) and virological (PCR, antigenemia and serology) examinations, with the first blood sample taken for HIV detection.^{5,13,23}

In newborns and infants under 18 months exposed to HIV, the detection of antibodies to this virus does not distinguish whether it is a passive (maternal IgG) or active (proper to being infected) immunity. Therefore, in this group of children, infection can only be confirmed if HIV or its components (nucleic acid, p24 antigen) is detected in blood or tissues.²³ The nucleic acid of the virus can be detected with the technique of PCR: HIV-DNA-PCR. With the application of this technique, a decrease in the age of confirmation or discarding of HIV infection was achieved from the age of 27 months before 1992, to the current age of 3 to 4 months. Depending on the samples that are positive, it will be possible to say whether the infection was acquired in utero or peripartum (see Tables 1&2). The fact that the first sample is taken before 48-72 hours of life (in other guidelines it is from 15 days of age) allows to determine the moment in which the infection occurs: in utero, a factor of poor prognosis for the evolution of the child, or late in pregnancy or peripartum, with a better prognosis.²¹

Table 1 Specific diagnostic sample in exposed newborns to HIV

1.	1st sample for HIV-DNA-PCR: taken before 48-72 hours of life (sample taken in neonatology)
2.	2nd sample for HIV-DNA-PCR: taken at 2-4 weeks of age ((or as soon as possible if the first sample is positive)
3.	3rd sample for HIV-DNA-PCR: take as soon as possible if the first and/or second sample is positive, and no later than 3 to 4 month if the first two are negative

Provided that the Exposed Newborn does not receive maternal or wet nurse feeding.

Table 2 Definition of HIV infection in children

Infection acquired in utero:	
1.	HIV-DNA-PCR before 48-72 hours of age: positive result
2.	Confirmed with following tests
Infection acquired intrapartum or very close to delivery:	
1.	HIV-DNA-PCR before 48-72 hours of age: negative result
2.	2nd sample (> 1 week old): positive result
3.	3rd sample: positive result confirming 2nd sample result

Provided that the Exposed Newborn does not receive maternal or wet nurse feeding.

Progress 1995 to date: Reduction of HIV VT from 35% before 1995 to <2% today in those binomials in HIV VTPP.

Knowing if a woman who becomes pregnant is already HIV (+) or detecting the infection in her during pregnancy allows the implementation of VTPP and largely prevents the birth of new infected children.

In Chile, the HIV VTPP implementation began in 1995 in hospitals, 10 years before the promulgation in 2005 of the Norm for the Prevention of Vertical Transmission of HIV by MINSAL; this Norm was updated in 2010 and 2013.¹³ According to the Norm of 2013, all pregnant women must be offered HIV testing at the first consultation; if the test is negative, but there are risk factors, do a 2nd test at week 32-34; currently in most hospitals a 2nd examination is done to all pregnant women, regardless of whether or not she have risk factors. If the woman goes into labor without having been tested (e.g. for uncontrolled pregnancy) an HIV test with a rapid result (ELISA or rapid test) should be done. Currently, a rapid test is also done to pregnant women whose only test carried out during pregnancy was negative.

Since 1995, the progressive implementation of HIV VTPP in mother-child binomials resulted in a significant reduction in VT from >35% prior to that date, without protocols, fell to 9.5% in 1997 only with Zidovudine as ARV in pregnant women, then to 2% in 2005 with bitherapy (Lamivudine + Zidovudine) and since then to the present, already with triterapia, it has fallen to <2%.¹³⁻¹⁵ In Chile, except for 2014 and 2015 when there were rates of mother-to-child transmission of HIV of 5.6% and 6.8%, in the following years the figures have been around 2%.

Progress: 1996 Start ART in all children where indicated.

In 1996, the use of ART was initiated in all children who were indicated, initially with bitherapy and since 1998 with tritherapy with the ARVs available at that time. There are currently 22 ARVs that have been approved for children <12 years and 4 more approved for adolescents, in whom, in addition, some co-formulated ARVs can be used.²⁴ Currently, ART consists of a tritherapy with a skeleton of 2 Nucleoside Reverse Transcriptase Inhibitors plus a third ARV that can be a Non-Nucleoside Reverse Transcriptase Inhibitor, a Protease Inhibitor, an Integrase Inhibitor or an Entry Inhibitor.²⁴⁻²⁷ According to all ART guidelines, children who are in clinical stage of AIDS and/or immunological stage 3 (severe immunosuppression) should receive ART, independent of viral load (VL).²⁴⁻²⁷ The indication for ART in children who are in other clinical and/or immunological stages has varied over time: from a later onset to an earlier one.

According to the guide that is about to be promulgated in Chile, ART should be indicated to children as soon as they are detected infected, regardless of their age, clinical stage, immunological stage and viral load (this is already being applied), ensuring adherence to therapy before starting it. At each check-up, adherence to and compliance with ART, tolerance, and adverse effects and drug interactions should be assessed. The effectiveness of ART was evidenced in clinical, immunological and virological improvement. The clinical improvement resulted in a decrease in infections, especially of primary opportunists, a better quality of life and a prolongation of survival, a prolongation that has allowed the appearance of opportunistic infections due to latent agents, such as tuberculosis, and cancers.^{18-20,22} As infections have decreased, deaths have also decreased and cancers have appeared as the cause of it. In 2014, 70% of the children detected were adolescents (18-20). At the end of July of 2022, 200 children and adolescents were monitored in

the Pediatric HIV/AIDS Care Program, SOCHIPE/MINSAL, all in ART. That is, of the 486 children and adolescents detected until the end of June 2022, practically 60% have already passed to adults. Of the children and adolescents in control, one-third are under 10 years old, one-third are between 10 and 14 years old, and one-third are over 15 years old.¹⁶

Paediatric programme of HIV/AIDS care Sochipe/ Minsal

When a newborn or child exposed to HIV or infected with HIV is detected, it must be notified to the MINSAL and communicated to the Pediatric Program of the Health Service or the corresponding Pediatric Hospital to which it will be sent. Prior to referral, the newborn undergoes a general and infectious clinical evaluation and and general and infectious laboratory tests are performed, and the first blood sample for HIV-DNA-PCR is taken in the 48-72 hours of life, Tables 1 & 3.^{5,13,23} In the management of newborn, due to the possibility of transmission of the virus by milk, breastfeeding and wet nurses must be suspended [in Chile the MINSAL, provides drugs to suspend breastfeeding and provides initiation formulas during the first 6 months of life to the children of HIV mother (+)]; after 6 months they remain in the National Complementary Feeding Program (Programa Nacional de Alimentación Complementaria: PNAC); the BCG vaccine is currently only placed if the result of the first sample of HIV-DNA-PCR is negative. In addition, preventive HIV VT ART should be initiated (only with Zidovudine or, in addition, if the pregnant woman has risk factors, with Zidovudine plus Nevirapine or Raltegravir).^{5,13}

Table 3 HIV Infection in Children Laboratory Diagnosis (ISP; December 1997)

Age children	Confirmed infection	Discarded infection
Newborn	At least 2 samples with PCR (+) without considering first sample (taken before 48 hours of life)	At least 2 samples with PCR (-) without considering first sample (taken before 48 hours of life)
Children 1 month and < 18 months	2 PCR must be (+)	2 PCR must be (-)
Children ≥18 months	1 PCR (+) and/or serology only (+) is sufficient	1 PCR (-) and/or serology (-) is sufficient

Provided that the Exposed Newborn does not receive maternal or wet nurse feeding.

In the Paediatric Programme, HIV-exposed newborns are followed until infection is confirmed or ruled out by the HIV-DNA-PCR technique. If HIV infection is ruled out, they are checked as a normal child, but the definitive discard is done with a serological HIV test at 12 and 18 months of age.^{5,13,23,27} If the infection is confirmed, they remain in the Programme.

In the Paediatric HIV/AIDS Care Programme the newborns with confirmed infection and infected children detected in postnatal remain under control until the age of 18 years, when they are transferred to the Adult Program. Figure 1 shows the flow chart of the Paediatric HIV/AIDS Care Programme. In the Paediatric Programme, newborns with confirmed infection and infected children detected in postnatal life are followed by periodic clinical assessment (general and by specialist) and laboratory examinations [general, infectological, immunological (quantification of immunoglobulins and CD4) and virological (viral load: VL)].^{5,13,30}

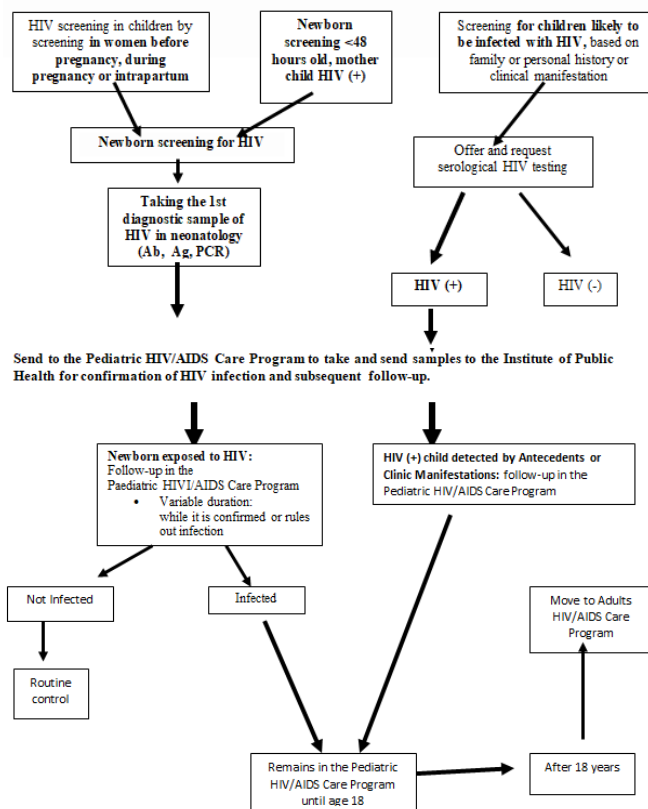


Figure 1 Flowchart pediatric HIV/AIDS care program.

Initial clinical and immunological (CD4) evaluation allows staging of HIV-infected children according to the 1994 CDC Classification.¹⁷ Periodic clinical, immunological and virological evaluation (CD4 and VL every 3-4 months) allows estimating the prognosis, adapting preventive management, monitoring the response to ART and making changes, if necessary.^{5,13,27} Management is multidisciplinary and includes preventive measures for opportunistic infections such as *Pneumocystis jirovecii* and indication of vaccines of the National Programme of Immunizations (Programa Nacional de Inmunizaciones: PNI) and Extra-PNI vaccines, therapeutic measures for complications of infection, and indication for ART.²⁸⁻³¹ The therapy of HIV infection that is initiated according to the Clinical Guidelines for Acquired Immunodeficiency Syndrome, HIV/AIDS, MINSAL (guidelines 2005, 2009, 2013),²⁷ is changing according to other international guidelines²⁴⁻²⁶ and this will be reflected in the new guidelines to be promulgated.

Discussion and conclusions

In Chile, the joint work since 1992 of the Committee on HIV/AIDS, SOCHIPE, with MINSAL in the HIV/AIDS Care Programme has, as already noted, achieved several advances in the control of children and adolescents infected with HIV. The diffusion of the topic throughout the country allowed an improvement in the screening with a decrease in the number of children detected in the AIDS stage from 41% in 2008 to 28% in 2014, and an increase in those detected in the year of birth from 33% before 2005 to 50% from 2006 to 2014 and 49% between 2015 y 2022.^{16,18-20} Detecting children in the year of birth, especially being younger than 3-6 months, means that there is a greater screening based on maternal history and / or admission to PPT. Those detected after 6 months of age and especially those older than 1 year may have been detected by clinical manifestations. Many of the

children screened after the year of their birth have been screened for being slow progressors who presented manifestations late.²¹

The application of the HIV-DNA- technique as a diagnostic tool for HIV in newborns and infants began to be applied in Chile much earlier than in other countries, reducing the age of confirmation or discarding of HIV infection to 3 to 4 months. The fact that the first sample is taken before 48-72 h of life (in other guidelines it is from 15 days of age) allows to determine the moment in which the infection occurs: in utero, a factor of poor prognosis for the evolution of the child, or late in the pregnancy or peripartum, of better prognosis.²¹ However, the increased use of preventive ART of VT may result in the first neonatal sample being negative.

HIV VTTP began to be applied in some hospitals in 1995, 10 years before the Norm, lowering the transmission of the virus in the binomials in protocol. The 2005 promulgation of the HIV Transmission Prevention Norm continues to decline, demonstrating its effectiveness.

The effectiveness of ART was evidenced in clinical, immunological and virological measurement. The clinical improvement resulted in a decrease in infections, especially opportunistic infections. Immunological improvement was evidenced in an increase in children in stage 1 from 11% to 70% and decrease in children in stage 3, from 67% to 8%, and virological improvement in achieving undetectable VL before 6 months of ART. All this has resulted in a prolongation of life and a decrease in deaths: in 2014 70% of the children detected were adolescents and currently of all children / adolescents detected from 1987 to date, 60% have already passed into adulthood.^{16,18-20}

Thanks to HIV PPTV, the first girl detected with HIV on VT now has 2 uninfected children. The same has happened with several of the first HIV-positive girls who have uninfected children thanks to VTTP.³²

There are still challenges to be solved. One is to achieve the goal set by the World Health Organization (WHO) and United Nations (UN)³³⁻³⁴ for 2020 of 90-90-90 for HIV/AIDS, what is it:

- I. 90% of people living with HIV know their HIV status.
- II. 90% of people diagnosed with HIV receive continuous ART.
- III. 90% of people who receive ART have viral suppression.

Achieving this goal will also reduce HIV VT. To achieve this, in Chile in 2019 not only the rapid test for HIV screening was implemented, but its coverage was increased and its access channels were expanded.

In Chile, VT of HIV is declining and approaching to the elimination goal established by the WHO and UN of <2% and < 50 cases/10 000 live newborn.

We are finished the year 2022 and the goal has not yet been reached in most countries, including Chile.

Failure to comply with VTTP, late control or lack of control of pregnancy, a negative result of the only HIV test carried out during pregnancy, the use of increasingly diverse ARVs in pregnant women with birth of children already infected with multi-resistance to some of them make it difficult to achieve this goal, and the problem of immigrants, especially Haitians, because of language and because they often have other infections concomitant with HIV, such as hepatitis.

A second HIV test in the third trimester of pregnancy, already incorporated as explicit health guarantees (Garantías Explícitas en

Salud: GES) and incorporated into the new MINSAL Norms and Guidelines, will contribute to achieving the goal set by WHO) and UN for the elimination of VIH VT.

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None.

Conflicts of interest

No conflicts of interest.

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