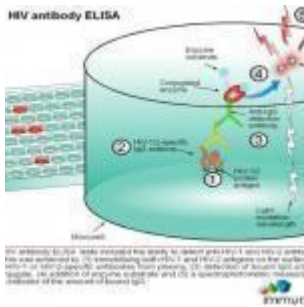


Eight month old boy with recurrent infections



- [Patient presentation](#)
- [History](#)
- [Differential Diagnosis](#)
- [Examination](#)
- [Investigations](#)
- [Discussion](#)
- [Treatment](#)
- [Case Final Outcome](#)
- [Evaluation - Questions & answers](#)

Patient presentation

An eight month old boy presented with failure to thrive and recurrent infections including dissemination of his BCG vaccination. [HIV ELISA test](#) was negative.

Acknowledgement

This case study was kindly provided by Dr Monika Esser MMed Paed, Head of Division of Immunology, N.H.L.S Coastal Branch, Tygerberg Hospital.

History

8 months old

- Child presented with failure to thrive, recurrent infections and dissemination of his BCG vaccination he received at birth.
- Blood tests showed a severe lymphopaenia which was confirmed by abnormal lymphocyte subsets and severely diminished mitogen proliferation.
- He had received all vaccinations up to this point with positive IgG antibodies present. – [Expanded Programme on Immunisation \(EPI\) schedule](#)
- HIV ELISA test was repeated and found to be negative.
- He was given the likely diagnosis of severe combined immunodeficiency disorder or SCID.
- The variable Immunoglobulin levels were presumed to be of maternal origin.
- The patient was isolated and barrier nursed on a standard SCID protocol and treated for disseminated BCG infection.

10 months old

- The mother was screened as a possible donor for bone marrow transplant, she tested HIV (+).
- PCR for HIV was done on the patient and he was found to be HIV (+).
- He was started on HAART therapy, 2 months after starting treatment for BCG dissemination.

16 months old

- After 6 months of HAART the patient's lymphocyte profile and mitogen responses normalised.
- Immunoglobulin levels rose to normal and remained at normal levels.
- Viral load was undetectable.
- He experienced no further serious infections, and remained HIV ELISA (-) at one year follow-up.

Important to note:

- A subsequent review of his hospital records revealed a previous admission with PCP pneumonia under a different birth date and registration number at 4 months of age.
- At the time he had a positive HIV PCR result. He was then lost to follow up until the admission at 8 months of age.
- Moderate lymphopaenia was noted at the 4 month admission.

Differential Diagnosis

- SCID
- Bone Marrow suppression
- HIV

Also consider causes of false-negative HIV antibody ELISA:

- Acute or early HIV infection (pre-seroconversion)
- Late stage HIV disease – seroreversion (severe immunodeficiency)
- Unusual HIV strain (HIV-1 group N, O or recombinant or certain HIV-2 strains)
- Immune complex formation
- Rheumatoid factor
- Severe combined immunodeficiency (SCID)
- B-cell disorder (agammaglobulaemia, common variable immunodeficiency)
- Immunosuppressive therapy
- Replacement transfusion
- Bone marrow transplant
- Laboratory glove starch powder
- Laboratory error

Examination

Ill looking child, severely malnourished.

Patient is failing to thrive, marasmic, measuring below the [5th centile for height and weight](#).

On General:

- Respiratory rate- 30 breaths per minute
- Temperature- 38°C
- Generalised lymphadenopathy

Respiratory Examination:

- Persistent productive cough
- Harrison's sulcus
- Bilateral lower lobe crepitations

Other systems:

Nil of note

Investigations

9 months old	18 months old	2yrs 1 months old	Controls and ref ranges	
CD3	139 uL	5 624 uL	11 579 uL	1 700 – 3 600
CD4	21 uL	1 499 uL	4 287 uL	1 700 – 2 800
CD8	119 uL	4 055 uL	5 946 uL	800 – 1 200
NK	226 uL	3 202 uL	3 669 uL	300 – 700
B cell	29 uL	317 uL	3 117 uL	500 – 1 500
PHA	394 counts/min	Results not available	15 743 counts/min	46 916 counts/min
Con A	2 081 counts/min	Results not available	2 967 counts/min	32 650 counts/min
Prot A	164 counts/min	Results not available	1 820 counts/min	40 612 counts/min

Phytohaemagglutinin (PHA) stimulates predominantly T-helper cell activity

Concanavalin A stimulates predominantly T-suppressor cell activity

Protein A stimulates B-cells.

(in acknowledgement of NHLS-Tygerberg Hospital)

	4mths	8mths	10mths	11mths	12mths	14mths	16mths	25mths
ELISA	(-)	(-)	(-)			(-)		(-)
PCR	(+)		(+)					
Viral Load				Log 5.93 Start of HAART	Log 3.8		Undetectable	

Discussion

There are two discussion parts to this case. Although the child does not have SCID as was initially thought we have included SCID in the first part of the discussion.

- Combined Immunodeficiencies (CID's) are characterized by defects in T-cell development and/or function which may be associated with abnormalities in the development of B and/or Natural Killer (NK) lymphocytes.
- Patients with SCID have the most severe form of T-cell depletion.
- Severe early onset infections, including uncontrolled BCG infection and growth failure are characteristic. Without early diagnosis and proper treatment including bone marrow transplantation most patients die within the first year of life.
- Even in normal fetuses and neonates T-cell function is impaired compared to adult functioning. This includes T-cell mediated cytotoxicity and T-cell help for B-cell

differentiation.

- Some of the inhibitory effects of HIV-1 infection on the immune system may even occur in HIV-exposed, but uninfected infants.
- In the early days of Paediatric HIV infections, prior to specific antibody testing, primary immunodeficiencies (PID) were included in the differential diagnosis of the recurrent infections observed. In this child the unfortunate duplication of hospital records led to an incorrect initial diagnosis of PID.
- The recovery of lymphocyte numbers and function on HAART confirmed the diagnosis of an acquired immunodeficiency.
- The persistence of a negative [HIV ELISA](#), with high viral loads and (+) [PCR's](#)
- once the immune response had normalised may have been due to bone marrow suppression or infection in utero (i.e. mother seroconverting before delivery). But these are speculative answers and remain to be explained.
- False negative ELISA's have been reported in situations of severe CD4 depletion, possibly reflecting a subnormal antibody response.

The most likely hypothesis in this case is the following:

- The mother had a primary HIV-1 infection during pregnancy most probably in the third trimester.
- The child was infected perinatally before maternal seroconversion.
- Hence, no placental transfer of maternal HIV-1 antibodies. (Also child is not breastfed or breastfeeding stops before seroconversion.)
- Severe immunodeficiency results in child due to HIV infection, hence no antibody response can be mounted.
- Mother is tested after seroconversion and is now ELISA pos.
- Child is HIV+ by PCR but not by ELISA (no antibodies

present).

- ARV treatment reduces viral load to below detection, lymphocyte responses appear normal.
- Subsequent ELISA testing remains negative due to lack of HIV antigen.

Treatment

Patient was treated with HAART and continued to see improvements. His viral load remained undetectable and his CD4 count continued to improve.

Final Outcome

Although patient has remained ELISA negative, he still remains PCR positive for HIV and has therefore remained HIV positive.

It is important to educate the family on this fact because they must understand that if they test their child for HIV at another facility they may be told that their child is HIV negative based on the ELISA test. However, their child is HIV positive and they must therefore not stop the ARVs, if they do there will be a resurgence of symptoms.

Evaluation – Questions & answers

What is the likely cause of this child having a negative ELISA in the face of a positive HIV PCR?

At this age there may no longer be any mother's antibodies circulating. Furthermore, this child was started on ARVs early in life (10 months) at a time when his own immune system was immature. Furthermore, the viral load was dropped so quickly with ARVs that it could not provide an antigen stimulus and therefore never had time to develop true antibodies to the virus. Resulting in a negative antibody response.

What is the importance of the Lymphocyte Proliferation Assay?

The Lymphocyte Proliferation Assay (LPA) is a test used to measure how well a person's immune system is functioning by testing the memory of T cells to recognise antigens or microbes. LPA can also be used to measure improvements in immunological function following antiretroviral therapy.

How do infants develop disseminated BCG?

Bacillus of Calmette and Guérin (BCG) is live attenuated Mycobacterium bovis, used as a vaccine against TB. In South Africa, BCG forms part of the Extended Programme of Immunisation (EPI) and is routinely given at birth. In immunocompetent patients this is a safe vaccine however immunodeficient patients may develop disseminated TB which has a high mortality rate.

How is disseminated BCG avoided?

BCG vaccination is contraindicated in infants with immunodeficiency but they are usually vaccinated prior to this diagnosis, and therefore cannot be avoided. However, in these cases it is important to note that siblings should not receive this vaccine.

What was the 1st generation HIV antibody ELISA test designed to detect?

This test was designed to detect anti-HIV-1 antibodies of the IgG isotype in plasma samples.

What was the 2nd generation HIV antibody ELISA test designed to detect?

This test was designed to detect anti-HIV-1 and anti-HIV-2 antibodies of the IgG isotype in plasma samples.

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What was the 3rd generation HIV antibody ELISA test designed to detect?

This test enhanced the sensitivity of the assay by including the detection of anti-IgM antibodies as well as IgG in plasma samples.

What was the 4th generation HIV antibody ELISA test designed to detect?

This is a combined test of 4th generation HIV antibody and p24 ELISA called the Combo test. This test enhances the sensitivity of the assay to detect early or acute HIV infection by including detection of p24 antigen in plasma samples. This combined test was designed to eliminate false negatives of the "window period" when antibodies are not yet detectable.