CASE STUDY

VIROLOGICAL RESPONSE WITHOUT CD4 RECOVERY

A case of disappearing soldiers – can basic science help?

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The objective of antiretroviral therapy (ART) is to suppress viral replication so that immune restoration can occur. Failure of immune restoration is usually associated with poor virological suppression. In children a good immunological and clinical response to ART is often achieved despite incomplete viral suppression. However, we have recently managed a number of children in whom immune restoration did not occur despite excellent virological suppression. We present a case, discuss possible causes and speculate on the appropriate course of action.

CASE DISCUSSION

A 5-year-old boy with WHO stage 3 HIV disease attends the Community Health Centre in Grabouw, approximately 100 km from Tygerberg Academic Hospital. He has been on appropriate doses for body weight of stavudine, lamivudine and efavirenz for the past 14 months. At baseline his plasma HIV RNA was 87 000 copies per ml (log 4.94) and the CD4 count was 263/µl (6.6%). He weighed 16 kg and his weight-for-age Z-score (WAZ) was –0.69. He had just completed his second month of antituberculosis (TB) therapy. TB was suspected because his mother had TB and he had a persistent cough.

Six months after starting HAART and 2 months after completing anti-TB therapy:

- The patient's weight remained 16 kg.
- Notably, he had features of chronic lung pathology and a chest radiograph showed generalised bronchiectasis.
- He had no intercurrent illnesses.
- He had attended the clinic for follow-up regularly, and although there was no objective means of measuring this, his compliance with medication (ART) seemed good and his mother (a seasonal farm worker) confirmed this. His TB treatment card showed good compliance with TB treatment.
- His viral load was undetectable.
- His CD4 count was now 258/µl (0.36%).
- A full blood count (FBC) and biochemistry (transaminases) were normal.

Two months later, **8 months** into highly active antiretroviral therapy (HAART), the tests were repeated:

- The patient had now lost a kilogram in body weight.
- His mother reported that he had been admitted to the regional hospital for 5 days for a 'chest infection'. He had received intravenous antibiotics but did not require supplemental oxygen. There was no letter documenting clinical findings, investigations or management during that episode.
- He had no constitutional or pulmonary symptoms, and had no excessive losses (e.g. diarrhoea). His appetite remained good and his nutritional intake at home had not changed in any form (he was also receiving nutritional supplements from the clinic).
- The only new finding was a crop of molluscum contagiosum on his left lower eyelid.
- On history, there were no known TB contacts in his immediate environment.
- The CD4 count was 181/µl (6.1%), and the total lymphocyte count (TLC) 4 700 $\times$ 10^6 cells/l.
- The viral load remained undetectable.
- The rest of the FBC was normal.

At this time the patient was **re-investigated for TB:**

- The tuberculin skin test was non-reactive
- A sputum smear for acid-fast bacilli was negative and TB cultures were negative after 42 days.
- A chest radiograph showed no new changes.

Over the following few months his weight increased to 17 kg. Treatment was adjusted to stavudine 20 mg capsules, lamivudine 75 mg (half a tablet) twice daily and efavirenz 250 mg capsule at night (reduced as he was no longer receiving rifampicin). His mother was shown how to use a pillbox in an

effort to assist with adherence to ART. Nutritional supplements were provided in an effort to improve his nutritional status.

Four months after the last set of tests and 12 months into HAART:

- There are no new clinical symptoms or signs, and the patient has had no serious illnesses during that period.
- Compliance with clinic visits and medication (as well as could be ascertained by means of pill counts and recall) remained good, and his mother is concerned and reasonably informed about his well-being and his CD4 count!
- His weight is 17 kg (WAZ –1.07) and height 104 cm (height-for-age Z-score –1.72, weight-for-height Z-score 0.09).
- The CD4 count is 164/µl (5.02%) and the TLC 5 900 × 10^6 cells/l.
- The viral load is undetectable.

Table I shows these results in chronological order.

TABLE I. LABORATORY AND ANTHROPOMETRIC RESULTS

Date	Viral load (copies per ml)	CD4 (cells/µl)	TLC (× 10^6) cells/l	Weight (kg)	WAZ
Baseline	87 000 (log 4.94)	263 (6.6%)	– –	16 kg	–0.69
6/12	Undetectable	258 (6.4%)	–	16 kg	–1.13
8/12	Undetectable	181 (6.1%)	4 700	15 kg	–1.29
12/12	Undetectable	164 (5.0%)	5 900	17 kg	–1.07

All the specimens were processed in the same laboratory, and with the exception of baseline samples were all taken by the same person.

Why is there no immunological recovery and worsening immunosuppression after one year of ART, although there is full viral suppression?

Why has the patient shown no improvement in growth at all?

POSSIBILITIES

- We did not suspect **hyperlactataemia/lactic acidosis**, so did not test for it. Also, the patient would need to travel about 60 km to the centre where this can be done.
- Does he have **incompletely treated TB** or resistant TB, which is contributing to his state of persistent immunosuppression? There is no evidence of radiological deterioration and he remains asymptomatic
- Does he have **an occult opportunistic infection or malignancy** that is contributing to his immunosuppression? Which one? Where? Nothing is clinically obvious. No palatal Kaposi's sarcoma lesions were seen. *Mycobacterium avium-intracellulare* infection is possible, yet there is no focus of infection. He has remained on co-trimoxazole throughout.
- His total lymphocyte count has remained normal. What's going on?

Where, oh where, have his soldiers gone?

DISCUSSION

This case illustrates the problem of **discordant immunological and virological response** to ART in a child. After 12 months he has shown a good virological response. Clinical response has been moderate. He has had no significant weight gain, but there have been no significant intercurrent illnesses. His CD4 count has declined persistently and significantly.

The usual response to HAART is viral suppression and immune reconstitution. Some patients, however, show discordance between virological and immunological responses. In children, a rise in the CD4 count despite detectable plasma HIV RNA occurs fairly commonly. The converse, virological response and the absence of immunological response, as in our patient, has been described in adults. Poor CD4 responses can occur with previous therapeutic failure, low baseline CD4+ T cells, advanced disease, poor adherence to HAART, long duration of therapy, and previous treatment interruption. So far there is no evidence that patient age or viral or genetic factors are implicated.[1]

Jevtovic and colleagues[2] in Serbia recently conducted a retrospective survey of discrepant values in a cohort of 446 adult patients. Almost half showed dissociation, with 39% not reaching a CD4 count of 400 cells/µl and 11% not reaching a count of 200 despite adequate viral suppression. The most important risk factor was a baseline CD4 count below 100/µl. They did not associate discordant results with adverse outcome. Protease inhibitors appeared to be protective, as they prevent CD4 loss through inhibition of apoptosis of CD4 cells.[3]

The situation in Serbia is analogous to that in South Africa where until recently lack of access to health care has resulted in initiating ART in patients with advanced disease, as described in the above case report.

As a means of evaluation, we ask and attempt to answer a series of questions about this case.

WHAT COULD ACCOUNT FOR SUCH A RESPONSE?

1. Poor adherence to HAART seems an unlikely cause. We think that the patient would not have achieved viral suppression if he had not been receiving his therapy.
2. Is his immunological response to HAART perhaps simply slow or delayed? This is uncommon in children, who in contrast to adults usually have good CD4 recovery in the face of incomplete viral suppression, with their thymic response and naïve T-cell recovery rate being 10 - 40 times

faster than that of adults in the second phase of immune restoration.[4] However, responses to ART show individual variation. In older children and those with baseline CD4% significantly below 10%, immunological recovery on HAART can be slow. Individuals who do not experience significant increases in CD4 cell levels may have initiated therapy after significant destruction to the thymus had already occurred.

3. Is the patient harbouring an occult opportunistic infection, leading to ongoing immune activation and thus poor clinical and immunological response? He was re-investigated for TB to exclude the possibility of incompletely treated or resistant TB. Another consideration was atypical mycobacterial infection, particularly *M. avium* complex (MAC). So far three sputa remain negative by smear and culture. There is no apparent clinical evidence of opportunistic malignancies such as Kaposi's sarcoma or lymphoma. Could bronchiectasis be playing a role? Recruitment of activated CD4 cells in bronchoalveolar lavage fluid has been observed in patients with pulmonary disease.[5]

4. Could immunosuppressive or myelosuppressive drugs have caused disturbance of bone marrow T-cell progenitor production? If so, why would it be a selective lymphocyte problem? There seems to be no evidence of myelosuppression; all the patient's blood cell indices, including his total lymphocyte count, were in the normal range. We did not ascertain whether the lymphocytes were T or B cells. If they are primarily B cells, it could mean that the thymus is severely impaired by HIV. The combination of tenofovir and didanosine has been associated with poor CD4 response but resolves with dose reduction of TFV. We are unaware of this type of response to other antiretrovirals.[6]

With no clear answers for the cause of this discordant response, we speculate on management options.

COULD THERE BE AN IMMUNOLOGICAL REASON?

It would seem that the patient has good HIV-specific immune responses, in that he has managed to suppress HIV replication to undetectable levels. He would probably then be a candidate for agents that enhance general immune activity, particularly those that induce T-lymphocyte differentiation and stimulate function, for example recombinant cytokines: interferon alpha (IFN), particularly pegylated IFN alpha-2, tumour necrosis factor (TNF) and interleukin-2 (IL-2). Cytokine dysregulation has been described in HIV-infected patients. Diminished IL-2 receptors on CD4 cells were described in 1991.[7] IL-2, a cytokine that stimulates the production of CD4 cells, has been proposed for patients who are unable to replenish CD4 cells, despite adequate viral suppression on HAART.[8] A number of trials have shown improvement in CD4 responses in adults with mild immunosuppression.[9] A possible mechanism for this response could be a diminished loss of CD4 cells through apoptosis.[10]

In anticipation of specific therapy, we continue to monitor the patient and seek to optimise his care.

WHAT CAN WE DO?

Immediate strategies that could help are to improve pulmonary care through physiotherapy, suppressive antibiotics, and excluding gastro-oesophageal reflux. This will reduce pulmonary inflammation and potential loss of activated CD4 cells in the lung. We will re-evaluate for reactive airways disease, where inhaled steroids may be very helpful. We will also consider switching from efavirenz to a protease inhibitor in the hope of diminishing CD4 apoptosis. A single drug switch is appropriate in a patient with undetectable plasma HIV RNA.

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