

## Long term recovery of IgG and IgM production during HIV infection in a patient with common variable immunodeficiency (CVID)

S Jolles, M Tyrer, M Johnson, D Webster

### Abstract

**Aims**—Common variable immunodeficiency (CVID) is the most common serious primary immunodeficiency. This paper describes the immunological consequences of human immunodeficiency virus (HIV) infection in a patient with familial CVID subsequently treated with highly active antiretroviral therapy (HAART).

**Methods**—Serial measurements over 11 years of serum immunoglobulins, specific antibodies to tetanus toxoid and pneumococcal polysaccharides, lymphocyte phenotypes, and HIV viral load were made.

**Results**—The patient recovered total serum IgG and IgM, but not IgA production, with adequate concentrations of specific antibodies, allowing withdrawal of intravenous immunoglobulin without an increase in infections. T cell numbers gradually declined and the patient developed a high grade B cell lymphoma. After successful chemotherapy, HAART was commenced, viral load fell from 472 000 to < 50 copies/ml, and CD4<sup>+</sup> T cell numbers increased from 13 to 661 × 10<sup>6</sup>/litre. Antibody production was maintained after suppression of viral load.

**Conclusions**—This is the first definitive report of reversal of IgG and IgM deficiency in familial CVID after HIV infection. Failure to normalise IgA supports the concept of separate predisposing genetic factors for selective IgA deficiency, which when combined with others lead to CVID. Furthermore, a persistently high viraemia is not required to maintain the recovery of immunoglobulin values, suggesting this depends either on a transitory effect of a high viral load, or a persistence of low amounts of virus.

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**Keywords:** common variable immunodeficiency; human immunodeficiency virus; seroconversion; highly active antiretroviral therapy

Common variable immunodeficiency (CVID) is the most common of the primary immunodeficiency disorders requiring immunoglobulin replacement, affecting about 1/25 000 in the white population. The characteristic feature is severe hypo-immunoglobulinaemia, predominantly affecting the IgG and IgA classes.<sup>1</sup> About 20% of patients have a first degree relative with either CVID or selective IgA deficiency (IgAD), demonstrating that these conditions are genetically linked.<sup>2</sup> Most patients

present with recurrent pyogenic sinopulmonary infections, which if not diagnosed early often progress to bronchiectasis. Patients are prone to gastrointestinal infection with *Giardia lamblia* and *Campylobacter jejuni*, although many patients have a chronic enteropathy in the absence of known pathogens. Other features include granulomatous involvement of various organs and autoimmune disease.<sup>3</sup> The mechanisms underlying CVID are not known but the evidence supports a combination of abnormalities in T cells and monocytes<sup>4</sup> and, in some cases, B cells.<sup>5</sup> A variety of T cell defects have been described, with clear evidence of a failure to generate antigen specific “memory” CD4<sup>+</sup> T cells after immunisation.<sup>4</sup> The current consensus is that a major subgroup of patients with CVID have a complex polygenic disorder of immune regulation, with one or more genes predisposing to the more common but less severe IgAD.<sup>6</sup>

### Methods

Circulating lymphocyte phenotypes (CD3<sup>+</sup>, CD4<sup>+</sup>, CD8<sup>+</sup>) were measured by standard flow cytometry analysis of whole blood. Immunoglobulin concentrations were determined by immunoturbidimetry (Hitachi 911; Roche). Specific IgG antibodies to tetanus toxoid (TT) and pneumococcal polysaccharide (PPS) (using Pneumovax containing 23 serotypes as antigen) were measured by enzyme linked immunosorbent assay (ELISA; Binding Site, Birmingham, UK). Ninety five per cent of adults have values > 8 and 26 mg/litre for TT and PPS, respectively. Human immunodeficiency virus (HIV) viral load was measured using the Roche Amplicor HIV 1 monitor v 1.5 ultrasensitive assay (Roche, Welwyn Garden City, UK).

### Results

A 27 year old homosexual man was referred in 1988 with recurrent infections and low immunoglobulin values: IgG < 2.4 g/litre (normal range 8-18), IgA < 0.4g/litre (0.9-2.8), and IgM < 0.24g/litre (0.6-1.9), but normal B cell numbers. He had a history of multiple chest and ear infections, epididymo-orchitis, diarrhoea, and cystic acne and had required surgery on six occasions for complications of otitis media and cholesteatoma. His 59 year old mother was also referred with low antibody values (IgG < 2.0 g/litre, IgA < 0.2 g/litre, IgM < 0.2 g/litre), normal B cell numbers, and a long history of recurrent chest, sinus, and urinary tract infections, in addition to childhood peritonitis and meningitis.

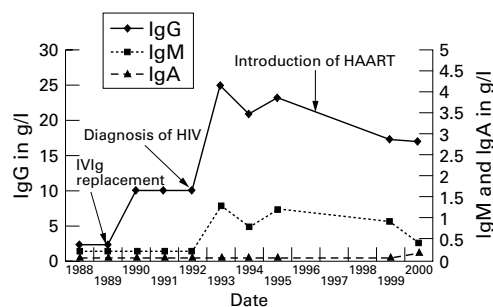
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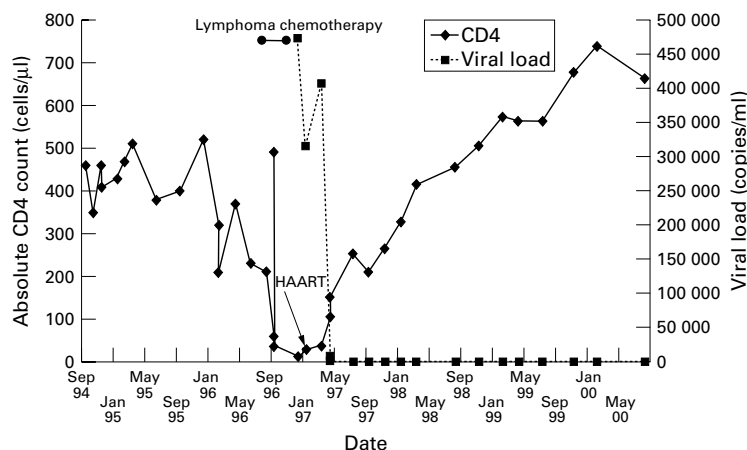


**Figure 1** Effects of human immunodeficiency virus (HIV) infection and highly active antiretroviral therapy (HAART) in a patient with CVID. Concentrations of IgG rise after intravenous immunoglobulin (IVIg) replacement (Sandoglobulin) (arrow). Before the diagnosis of HIV infection (arrow), there is a further rise in IgG with increasing IgM, but not IgA. IVIg treatment is discontinued, and later the introduction of HAART (arrow) results in a fall in viral load to undetectable values. However, immunoglobulin concentrations stay raised.

Both were diagnosed with CVID and commenced on intravenous immunoglobulin (IVIg) replacement (Sandoglobulin®) at 0.2 g/kg every two weeks. They responded well with reduced infective episodes. IgG concentrations were maintained at > 8 g/litre in both patients. Other family members had normal immunoglobulin concentrations.

The patient had stable IgG values on IVIg for the next three years, but in 1994 his IgG increased to 24.9 g/litre and IgM rose to 1.3 g/litre, with IgA and IgE remaining unrecordable (fig 1). He was investigated for HIV infection and was seropositive and P24 antigen positive at > 400 pg/ml. In view of the hypergammaglobulinaemia, it was decided to discontinue IVIg after an observation period of several months. Two months later his "baseline" concentrations of specific antibodies to TT and PPS were 22 and 27 mg/litre, respectively. The patient had no increase in infections and early antiretroviral treatment was not given in view of his good health, reluctance to take medication, and stable CD4<sup>+</sup> count (460 × 10<sup>6</sup>/litre).

Twenty one months later he complained of lower abdominal pain and an abnormal soft tissue mass was demonstrated in the right iliac fossa; histology confirmed a high grade B cell



**Figure 2** CD4<sup>+</sup> T cell reconstitution and viral load after highly active antiretroviral therapy (HAART).

lymphoma, which was Epstein-Barr virus negative. The patient received six cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone), which were well tolerated. His serum IgG antibodies to TT and PPS were low (12 and < 11 mg/litre, respectively). After recovery from chemotherapy, highly active antiretroviral therapy (HAART) was begun (stavudine 40 mg twice daily (bd), lamivudine 150 mg bd, and zidovudine 600 mg bd. Lamivudine was switched to didanosine (40 mg bd) after one month owing to aesthenia and hair loss. The HIV viral load fell from 472 000 to < 50 copies/ml (Roche Amplicor HIV 1 monitor v 1.5 ultrasensitive assay) over 12 months. His CD4<sup>+</sup> count steadily increased from 13 × 10<sup>6</sup>/litre in December 1996 to its highest value in March 2000 (736 × 10<sup>6</sup>/litre; fig 2). The CD4<sup>+</sup> percentage (27%; normal range, 24–48%) had normalised and the CD4<sup>+</sup>/CD8<sup>+</sup> ratio was almost normal at 0.6 (normal range, 0.7–3.5). During the period between the diagnosis of lymphoma and the present day, his IgG antibodies to TT have varied from 2 mg/litre to a current value of 23 mg/litre; he had received a booster immunisation with TT four years before the diagnosis of HIV, and again four years after discontinuing IVIg treatment, the latter accounting for the recent rise. Antibodies to PPS have been generally low (< 10 mg/litre), although on one occasion they rose to 35 mg/litre, possibly reflecting a transient response to infection. Anti-blood group B IgM titre was 1:8 (normal value, > 1:16). Six years after the diagnosis of HIV infection, he remains well on HAART and without IVIg treatment.

## Discussion

This is the fourth reported patient with CVID in whom antibody production has recovered after HIV infection.<sup>7–9</sup> He is the first patient who has been treated with HAART and these results establish that HIV can substantially reverse the familial type of CVID. It appears that continuously high HIV viraemia is not required to reverse the hypogammaglobulinaemia in familial CVID. However, HIV persists in both CD4<sup>+</sup> T cells and the follicular dendritic cells of the germinal centres despite HAART,<sup>10–12</sup> and may be required for long term recovery of immunoglobulin production.

Our patient, in keeping with two of three previous cases, showed recovery in only IgG and IgM production, with the serum IgA concentration remaining unrecordable. This is compatible with the concept that there are specific genetic, and possibly environmental, factors that are required to induce CVID on the background of IgAD. This view is supported by reports of CVID developing in patients with long standing IgAD.<sup>6</sup> The immunoglobulin and specific antibody values must be interpreted in the light of lymphoma and cytotoxic chemotherapy, both causes of secondary immunodeficiency.

It is interesting that our patient recovered the ability to produce IgG antibodies to TT, initially without "booster" immunisation, because most CVID patients have no measurable

antibody and fail to generate memory T cells after vaccination with protein antigens.<sup>4</sup> The observation that the immunodeficiency in CVID can be substantially reversed by HIV infection should encourage research into the mechanism responsible for this phenomenon.

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