IgG abnormalities in HIV-positive Malawian women initiating antiretroviral therapy during pregnancy persist after 24 months of treatment

Silvia Baroncelli[a,*], Clementina Maria Galluzzo[a], Giuseppe Liotta[b], Stefano Orlando[b], Fausto Ciccacci[b], Mauro Andreotti[a], Robert Mpwhere[c], Richard Luhanga[c], Jean Baptiste Sagno[c], Roberta Amici[a], Maria Cristina Marazzi[d], Marina Giuliano[a]

[a] National Centre for Global Health, Istituto Superiore di Sanità, Viale Regina Elena, 299, 00161 Rome, Italy
[b] Department of Biomedicine and Prevention, University of Rome Tor Vergata, Via Montpellier, 1, 00133 Rome, Italy
[c] DREAM Program, Community of S. Egidio, PO Box 30355, Blantyre, Malawi
[d] Department of Human Sciences, LUMSA University, Via Traspontina 21, 00193 Rome, Italy

A R T I C L E   I N F O

A B S T R A C T

Objectives: Hypergammaglobulinemia and anomalies in the IgG subclass distribution are common in HIV-infected individuals and persist even after many years of antiretroviral therapy (ART). The aim of this study was to investigate the IgG profile and dynamics in pregnant HIV-infected Malawian women in the Option B era.

Methods: Thirty-seven treatment-naive women received ART from the third trimester of pregnancy to 6 months post delivery (end of the breastfeeding period). ART continuation (group C) or interruption (group I) was then decided on the basis of the CD4+ cell count at enrolment (>350 or ≤350/μl). Total IgG and IgG subclasses were determined in maternal serum using a nephelometric assay at baseline and at 6 and 24 months postpartum.

Results: At enrolment, 36/37 women had IgG levels >15 g/l and there was a predominance of the IgG1 isotype (more than 90%) in parallel with underrepresentation of IgG2 (5.0%). After 6 months of ART, both groups showed a significant median decrease in total IgG (−3.1 g/l in group I, −3.5 g/l in group C) and in IgG1 (−4.0 g/l and −3.6 g/l, respectively), but only a modest recovery in IgG2 levels (+0.16 in group I, +0.14 g/l in group C). At month 24, hypergammaglobulinemia was still present in 73.7% of women in group C, although a significant reduction was observed in total IgG level and in IgG1 and IgG3 subclasses (p < 0.0001 in all cases). IgG2 levels did not show any significant change. In group I at 24 months, total IgG and IgG subclasses had returned to levels comparable to those at baseline.

Conclusions: The beneficial effects of 24 months of ART appear to be limited in the B-cell compartment, with an incomplete reduction of total IgG levels and no recovery of IgG2 depletion. A short ART period did not have significant effects on IgG abnormalities in women who interrupted treatment.

Introduction

Anomalies in the B-cell compartment have been described in all the phases of HIV infection, with hypergammaglobulinemia and defects in memory B-cells being the two most consistent observations (Pensieroso et al., 2013; Moir and Fauci, 2017). The mechanisms inducing immunoglobulin dysregulation are only partially known and are probably a consequence of systemic immune activation and the unbalanced production of proinflammatory cytokines, reflecting the T-cell dysfunction (De Milito et al., 2004; Titanji et al., 2006; Moir and Fauci, 2008).

The beneficial effects of antiretroviral therapy (ART) in reversing the immunological T-cell dysfunction are also extended to the improvement of B-cell compartment disorders (Amu et al., 2014), but there are contrasting results regarding the timing and quality of this normalization. Although a reduction in the hypergammaglobulinemia after ART initiation is widely described (Notermans et al., 2001; Serpa et al., 2010), most of the studies have reported the persistence of a chronic state of B-cell hyperactivation (Regidor et al., 2011; Pogliaghi et al., 2015), consistent with the

---

* Corresponding author.
E-mail address: silvia.baroncelli@iss.it (S. Baroncelli).

incomplete recovery of the immunological function observed in the T-cell compartment.

Even after many years of ART, B-cell compartment anomalies have been observed in aviremic patients (Chong et al., 2004; d'Orsogna et al., 2007; Hu et al., 2015; Pogliaghi et al., 2015) with IgG levels exceeding reference limits. In particular, the polyclonal B-cell activation causes an unbalanced IgG subclass profile with significant elevation of IgG1 and IgG3 levels and underrepresentation of the IgG2 isotype (Raux et al., 2000; McGowan et al., 2006). The combination of these abnormalities in IgG levels and distribution has been associated with a poor responsiveness to vaccinations in adults and children (Cagigi et al., 2010) and to a higher incidence of B-cell malignancies observed in HIV ART-treated patients (Bohlius et al., 2009; Hentrich and Barta, 2016).

In HIV pregnancy, the dysregulation of B-cells, and in particular maternal hypergammaglobulinemia, has a significant impact on IgG transfer from mother to foetus (Palmeira et al., 2012), causing a saturation of FcRN receptors, which have a key role in transplacental passage (de Moraes-Pinto et al., 1998). A reduced IgG concentration in the cord of neonates from mothers with IgG levels of >15 g/l and inadequate levels of specific IgG of maternal origin has been extensively reported in HIV-exposed infants (Cumberland et al., 2007; Babakhanyan et al., 2016).

In the last decade, ART administration to HIV-positive women during pregnancy and the breastfeeding period has resulted in a strong reduction in the rate of vertical transmission (Joint United Nations HIV/AIDS Programme, 2017); this in turn has led to an increasing rate of HIV-exposed uninfected (HEU) children, who nevertheless have a significantly higher rate of morbidity and mortality in the first years of life compared to their unexposed counterparts (Brennan et al., 2016). Efforts made towards understanding the higher vulnerability of HEU children are still inconclusive.

In this context, a maternal IgG disorder can have a critical role considering the importance of maternal immunological protection during the first 6 months of life, when the humoral responses to infections are mostly sustained by IgG of maternal origin (Simon et al., 2015).

In this study involving Malawian HIV-positive pregnant women in the Option B era, the aims were (1) to monitor the magnitude and the timing of total IgG and IgG subclass normalization (if any) after 24 months of ART, and (2) to determine the durability of the beneficial effects of ART on plasma IgG levels and the distribution of the subclasses in women who interrupted ART after 6 months and were followed up to 24 months.

Materials and methods

Study population

This study forms part of a larger observational study (enrolment during February 2008 to February 2009) aimed at assessing the safety and efficacy of ART administration in Malawian HIV-positive pregnant women (Safe Milk for African Children (SMAC) study) (Giuliano et al., 2013). The study was conducted in Malawi (Blantyre and Lilongwe sites) within the DREAM (Drug Resource Enhancement against AIDS and Malnutrition) Program of the Community of S. Egidio, an Italian faith-based non-governmental organization.

In this study, treatment-naive HIV-infected pregnant women started ART during pregnancy: in the presence of a CD4+ cell count <350 cells/µl, they received a combination of stavudine (30 mg twice daily), lamivudine (150 mg twice daily), and nevirapine (200 mg twice daily) as soon as possible after the first trimester and continued it indefinitely (group C, continuous therapy); or, in the case of a CD4+ count >350/µl, they received zidovudine (300 mg

twice daily), lamivudine, and nevirapine from week 26 of gestation until 6 months postpartum (group I, interruption of treatment). Women were instructed to exclusively breastfeed up to 6 months. After delivery, the mothers were visited monthly for clinical and laboratory assessment up to 24 months postpartum. Haemato-chemistry and viro-immunological analyses were performed at the local DREAM laboratories in Malawi. Women were included in this sub-study if they breastfed their infants for the scheduled 6 months and had plasma samples available at enrolment (before ART) and at 6 and 24 months post delivery.

Plasma IgG levels and IgG subclasses

Maternal total IgG and subclass plasma levels were determined using IgG total, IgG1, IgG2, IgG3, and IgG4 reagents (Siements; Siemens Healthcare Diagnostics) and read by automated nephelometry (BN ProSpec System Analyzer; Siemens Healthcare Diagnostics).

Statistical analysis

IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analyses. Results are presented as the median values with interquartile range (IQR) or percentages. Differences were evaluated using the Chi-square test or Fisher's exact test, as appropriate, for categorical variables, and by Mann–Whitney U-test for quantitative variables. Longitudinal differences were detected using the Wilcoxon test, and Spearman's correlation coefficient was used for the correlation analysis between quantitative variables. Differences were considered statistically significant when $p < 0.05$.

Ethical considerations

Ethical approval was obtained from the National Health Research Committee in Malawi (approval number #486), and informed consent was obtained from all individual participants included in the study.

Results

The characteristics of the two groups of women (group I, interruption of treatment, $n = 18$; group C, continuous therapy, $n = 19$) are reported in Table 1. Group C women were older ($p = 0.022$), with higher HIV-RNA levels ($p = 0.020$), and with a more immunocompromised profile. The median time of ART during pregnancy was 9.0 weeks, with a slight difference between the groups (group I: 7.0 weeks, IQR 4.5–13.0 weeks; group C: 10 weeks, IQR 8.0–15.0 weeks; $p = 0.051$). After vaginal delivery, all women continued the therapy for 6 the months of exclusive breastfeeding.

IgG levels and immunological parameters before ART initiation

At enrolment, the total IgG concentration was >15 g/l for all but one woman, with median levels of 24.1 g/l in group I and 27.8 g/l in group C, and no statistically significant difference between the groups ($p = 0.221$). The composition of IgG subclasses showed a predominance of the IgG1 isotype, which accounted for more than 90% in both groups, as well as an underrepresentation of IgG2 (5.2%) (Table 1). Although no significant differences were observed in IgG levels between the groups, a strong inverse correlation was found between total IgG levels and the CD4+ cell count ($r = -0.426$, $p = 0.009$; Figure 1). The association with CD4+ cells was also confirmed for IgG1 and IgG3 plasma levels ($r = -0.419$, $p = 0.010$; $r = -0.340$, $p = 0.039$, respectively), but not for IgG2 or IgG4 levels.

Table 1
Patient characteristics at enrolment; values are expressed as the median (interquartile range), or percentage.

	All	Group I	Group C	*p*-Value
Number	37	18	19	
Age (years)	27.0 (23.0–32.0)	23.5 (20.8–30.0)	30.0 (25.0–33.0)	0.022
Weight (kg)	57.0 (49.0–62.7)	56.9 (50.6–60.8)	57.3 (47.4–64.0)	0.855
Haemoglobin (g/dl)	10.3 (9.5–11.1)	10.6 (9.8–11.5)	9.8 (9.1–10.0)	0.142
WHO classification, I/II/III (%)	78.4/13.5/8.1	94.4/5.6/0.0	63.1/21.1/15.8	0.060
ART during pregnancy (weeks)	9.0 (7.0–13.0)	7.0 (4.5–13.0)	10 (8.0–15.0)	0.051
CD4+ (cells/μl)	340 (214–503)	503 (401–776)	223 (152–302)	<0.0001
HIV RNA (log copies/ml)	4.17 (3.49–4.69)	3.74 (3.51–4.46)	4.54 (3.78–4.75)	0.020
IgG total (g/l)	25.1 (21.2–29.3)	24.1 (19.5–27.7)	27.8 (21.3–30.9)	0.221
IgG1 (g/l)	23.5 (18.6–28.4)	22.2 (16.8–26.3)	25.3 (18.9–28.3)	0.245
Proportion of total IgG (%)	91.8 (87.5–93.9)	92.3 (87.4–93.6)	91.6 (87.6–94.6)	
IgG2 (g/l)	1.44 (0.96–1.82)	1.38 (0.93–1.81)	1.57 (0.94–1.85)	0.753
Proportion of total IgG (%)	5.2 (3.9–7.8)	5.4 (4.2–8.0)	5.8 (3.4–7.6)	
IgG3 (g/l)	1.30 (1.07–1.78)	1.21 (0.80–1.76)	1.41 (1.11–1.91)	0.298
Proportion of total IgG (%)	5.3 (4.4–6.4)	5.0 (3.7–6.3)	5.9 (4.6–6.6)	
IgG4 (g/l)	0.34 (0.14–0.45)	0.31 (0.12–0.44)	0.35 (0.20–0.47)	0.343
Proportion of total IgG (%)	1.36 (0.69–1.58)	1.4 (0.3–1.7)	1.4 (0.8–1.5)	

WHO, World Health Organization; ART, antiretroviral therapy.

Changes in IgG profile after 6 months of ART, at the end of the breastfeeding period

At 6 months, significant improvements in the viro-immuno-logical parameters were observed in both groups, and HIV-RNA plasma levels became undetectable in most women (group I: *n* = 15, 83.3%; group C: *n* = 16, 84.3%). The CD4+ cell count increased significantly from baseline in both groups (group I: +204 cells/μl; group C: +182 cells/μl), and the CD4+ count remained below 350 cells/μl in only seven of the 37 women.

However, hypergammaglobulinemia was still present in 34 of the 37 women, even though a significant decrease in total IgG levels was observed in both groups (group I: −6.5 g/l, IQR −3.1 to +0.05, *p* = 0.010; group C: −8.0 g/l, IQR −3.5 to −0.50, *p* = 0.006; Table 2, Figure 2). Regarding the subclass composition, the trend in changes was similar in the two groups, with some difference: while a significant decrease in the cytophilic isotype (IgG1 and IgG3) levels was observed in group I (IgG1, *p* = 0.004; IgG3, *p* = 0.016) and in group C (IgG1, *p* < 0.0001; IgG3, *p* < 0.0001), IgG2 levels showed a modest increase that reached statistical significance only for the women in group I (*p* = 0.003). IgG4 levels decreased minimally (statistically significant only in group I, *p* = 0.031).

The 6–24-month period

According to the Option B strategy, only group C, including women with a more severe viro-immunological profile at enrolment, continued ART after the breastfeeding period. In this group, all women reached HIV-RNA <50 copies/ml and a CD4+ count >350 cells/μl (median 560 cells/μl, IQR 420–730 cells/μl) after 24 months of treatment. The levels of total IgG decreased between 6 and 24 months, but after 2 years, 14 of 19 women (73.7%) still had hypergammaglobulinemia, with a median IgG level of 19.0 g/l (IQR 14.3–23.7 g/l). The decrease in total IgG was paralleled by a significant decrease in IgG1 levels (−2.3 g/l, *p* < 0.0001) and a less pronounced decrease in IgG3 (−0.23 g/l, *p* = 0.453) and IgG4 (−0.04 g/l, *p* = 0.004). IgG2 levels did not show any significant change, and after 24 months of ART treatment no recovery was observed in plasma and the IgG2 isotype remained largely underrepresented.

As expected, 15 of 18 women in group I were viremic at month 24 (HIV-RNA median 3.42 log copies/ml), while the CD4+ cell count remained stable with a median of 629 cells/μl (+66 cells/μl, IQR −21.3 to +307 cells/l; *p* = 0.05) with respect to pre-ART values. All women in this group had an IgG concentration >15 g/l at 2 years postpartum. The median level of IgG returned to values similar to those pre-ART (24.9 g/l vs. 24.1 g/l; *p* = 0.616), with no variation in subclass distribution.

Discussion

These results show that in HIV-positive pregnant women, 24 months of ART can improve the IgG abnormalities, but is not sufficient to normalize the IgG hyper production or to restore the normal subclass distribution. Overall, 24 months of ART had no impact on the IgG2 levels, which remained strongly underrepresented. It was also found that a short period of ART (about 7–10 months), although associated with a temporary improvement in IgG anomalies, was not sufficient to maintain these changes over 2 years postpartum.

Polyclonal hypergammaglobulinemia occurs in the setting of HIV infection (Cagigi et al., 2008), caused by T-cell dysregulation and by a direct interaction between mature B-cells and virions (Moir and Fauci, 2008). Many studies have reported that ART can partially reverse some immunological dysfunction of the B-cell compartment (Chong et al., 2004; Redgrave et al., 2005; Abudulai et al., 2016), decreasing the IgG hyperproduction over a variable interval of time, depending mostly on the time since HIV primary
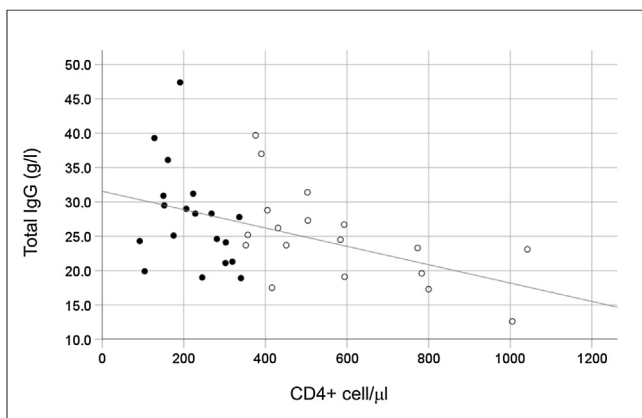

Figure 1. Correlation between the CD4+ cell count (cells/μl) and total IgG levels (g/l) in HIV-positive pregnant Malawian women before ART initiation (*r* = −0.426, *p* = 0.009). Group I: white dots; group C: black dots.

Table 2
Patient viro-immunological characteristics at 6 and 24 months postpartum; values are reported as the median (interquartile range), or percentage.

	6 Months		24 Months	
	Group I (n = 18)	Group C (n = 19)	Group I (n = 18)	Group C (n = 19)
ART regimen	AZT 3TC NVP	d4T 3TC NVP	None	d4T 3TC NVP
CD4+ (cells/μl)	733 (585–940)	402 (333–539)	629 (492–875)	560 (420–734)
CD4+ increase (cells/μl)	+204 (50–366)	+182 (116–271)	−35 (−191 to +47.5)	+197 (91–258)
HIV RNA > 50 copies/ml, n (%)	3 (16.7%)	3 (15.7%)	15 (83.3%)	0 (0%)
IgG total (g/l)	20.5 (17.9–22.5)	21.1 (18.8–28.2)	24.9 (21.4–27.8)	19.0 (14.3–23.7)
Patients with IgG >15 g/l (%)	15/18 (83.3%)	19/19 (100%)	18/18 (100%)	14/19 (73.7%)
IgG1 (g/l)	17.5 (15.7–20.3)	19.4 (15.9–25.6)	23.6 (19.2–27.4)	16.4 (12.8–21.6)
IgG1 change (g/l)	−4.0 (−8.6 to +0.2)	−3.6 (−8.3 to −1.4)	+3.7 (+1.5 to +8.4)	−2.3 (−5.4 to −0.7)
IgG2 (g/l)	1.47 (1.25–1.89)	1.59 (1.15–2.20)	1.36 (1.13–1.77)	1.43 (1.20–2.13)
IgG2 change (g/l)	+0.16 (+0.05 to +0.27)	+0.14 (−0.04 to +0.40)	−0.11 (−0.46 to +0.07)	−0.20 (−0.17 to +0.05)
IgG3 (g/l	1.02 (0.61–1.31)	1.10 (0.79–1.41)	1.10 (0.83–150)	0.97 (0.8–1.34)
IgG3 change (g/l)	−0.25 (−0.52 to +0.03)	−0.23 (−0.50 to −0.09)	+0.03 (−0.10 to +0.33)	−0.23 (−0.50 to −0.09)
IgG4 (g/l)	0.19 (0.12–0.32)	0.27 (0.14–0.34)	0.23 (0.13–0.33)	0.21 (0.12–0.34)
IgG4 change (g/l)	−0.02 (−0.19 to +0.11)	−0.04 (−0.12 to +0.02)	+0.02 (−0.46 to +0.03)	−0.04 (−0.10 to +0.00)

ART, antiretroviral therapy; AZT, zidovudine; 3TC, lamivudine; NVP, nevirapine; d4T, stavudine.

infection (Pensieroso et al. 2009; Moir et al., 2010). Although the majority of these studies involved patients from developed countries, where better sanitary conditions, a lack of chronic parasite infections, and the wider availability of different therapeutic approaches can have an important impact, analogous effects of ART on the memory B-cells and activation of B-specific markers have been observed in the few studies performed in African cohorts, reporting incomplete recovery of the B-cell anomalies induced by HIV (Longwe et al., 2010; Tanko et al., 2017).

This study focused on the IgG profile, since hypergammaglobulinemia in pregnancy has been associated with severe impairment of transplacental passage and can have important consequences for the clinical outcome of the infants (Abu-Raya et al., 2016). In a previous study involving women in the SMAC study, with ART initiated at week 26 of gestation, we correlated the high IgG levels of mothers at delivery to the reduced IgG levels observed in their 1-month old infants (Baroncelli et al., 2018). We concluded that the short period of ART exposure may not be sufficient for maternal IgG normalization. Here we extended the study to 24 months of observation in an attempt to better understand the dynamics of IgG levels and distribution in African HIV-positive pregnant women receiving ART. The inclusion of women who interrupted therapy according to the Option B strategy gave us the opportunity to explore the durability of the beneficial effects of ART on the IgG levels.

At baseline, HIV-positive, treatment-naïve women had median levels of IgG as high as 25.1 g/l, confirming that hypergammaglobulinemia is common in the HIV-infected African population, as already reported by us and by others (de Moraes-Pinto et al., 1998; Baroncelli et al., 2018). It was also found that the high levels of total IgG and IgG1 were not associated with the viral burden, but rather with the CD4+ cell count, suggesting that the T-cell dysfunction could be the primary force leading to the general dysregulation of the immune system (Malaspina et al., 2003). These results are in agreement with those of previous studies that have found IgG abnormalities associated with markers of immunoactivation and to the decline in T-cell functionality (Abudulai et al., 2016 D'Orsogna et al., 2007; Tanko et al., 2017). The IgG isotype distribution was dominated by IgG1, which represented more than 90% of total IgG, followed by IgG3 (5.3%), while the IgG2 isotype, which accounts for 20–30% of total IgG in the normal population (Vidarsson et al., 2014; Puissant-Lubrano et al., 2015), accounted for only 5.2%. The polarization of immunoglobulins towards the IgG1 and IgG3 subclasses is a characteristic of HIV-induced B-cell dysregulation (Raux et al., 2000), but we cannot exclude that the predominance of the cytophilic isotype in women could also be a

consequence of exposure to malaria infection, which in Malawi has a prevalence of around 24% in the general population (National Malaria Control Programme (NMCP) and ICF, 2018). Cytophilic antibodies mediate parasite-killing responses (Scopel et al., 2006), and their increase in populations living in areas endemic for *Plasmodium falciparum* has been widely reported (Rouhani et al., 2015; Dobaño et al., 2019).

The longitudinal monitoring of the IgG profile showed a significant reduction in total IgG, IgG1, IgG3, and IgG4 levels in the women in both groups after 6 months of ART. Nevertheless, only a small percentage of women (8.1%) reached IgG levels below the clinical cut-off indicating hypergammaglobulinemia, while most of them reached viral load suppression and a CD4+ cell recovery of >350 cell/μl. The significant trend in reduction of IgG and isotypes IgG1, IgG3, and IgG4 (but not IgG2) was similar in the two groups, indicating the beneficial effects of 6 months of ART also in women starting with a more compromised viro-immunological profile. However, 6 months of ART had no effect on IgG2 levels in group C women, and was associated with a modest increase in group I women that, although statistically significant, did not seem to be of clinical relevance.

In women on continuous therapy, a slow but statistically significant progressive decrease in total IgG and IgG1 continued, although 73.7% of women still had IgG levels above 15 g/l at 24 months postpartum, and no significant improvement was observed in terms of subclass proportions. Again IgG2 levels did not change with ART, remaining at the pre-therapy levels. In agreement with others (Tanko et al., 2017), it was found that the persistence of IgG disorders was not associated with the viral load (undetectable in all women). Indexes of immune activation were not measured in the study women, but it is likely that the persistence of inflammatory cytokines, a hallmark of HIV-induced immune activation status (Brenchley et al., 2006; Mehraj et al., 2019), could have affected IgG isotype switching (Tangye et al., 2002) and subclass synthesis (Kawano et al., 1994).

It is interesting to note that the beneficial effect of ART on IgG levels in group I women was only transitory, and 18 months after the interruption of ART all women had pre-ART IgG values, while the CD4+ cell counts remained higher with respect to baseline. Although functional tests were not performed, the study results confirm that the humoral dysfunctions in patients treated with ART have a differential timing in recovery with respect to CD4+ cells, probably depending on the patient's initial immunological condition (d'Orsogna et al., 2007; Moir et al., 2010; Pensieroso et al., 2009).

This study has several limitations. The patient sample size was limited, but the low degree of variability in IgG measurements
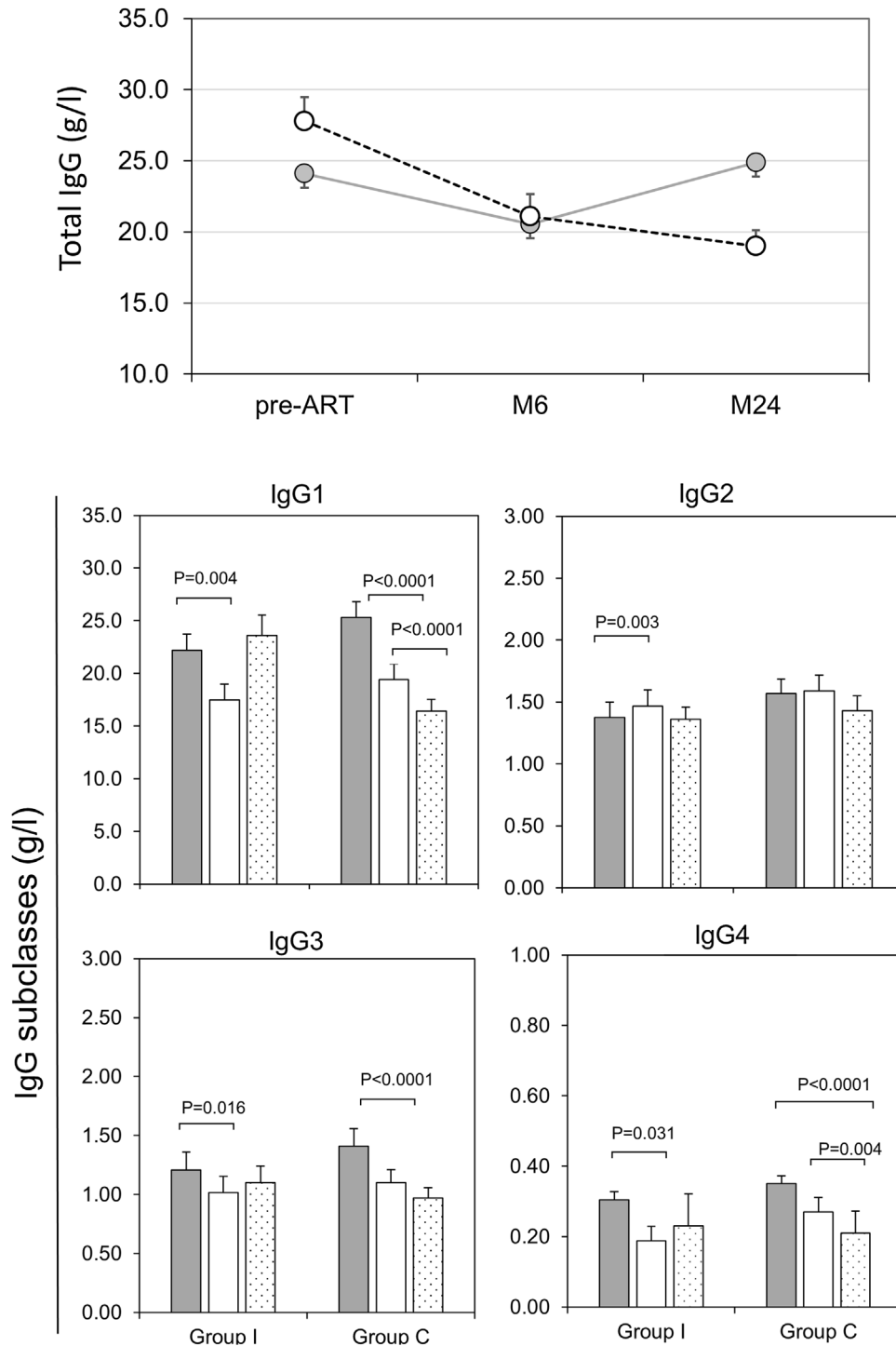
Figure 2. Longitudinal changes in total IgG and subclasses. Values are expressed as the median + standard error. (A) Trend of total IgG levels; group I grey dots, group C white dots. Graphs B–E show the IgG subclass levels. Grey bars: T1 (pre-ART); white bars: month 6 (end of breastfeeding period); dotted bars: month 24 (end of study period).

allows us to be quite confident regarding the validity of the data. Unfortunately it was not possible to perform functional tests on the B-cell compartment, which would have allowed a more complete analysis of the humoral dysfunction. Further, IgG reference ranges based mostly on Western population values were used, which can differ from those of African populations (Pieters et al., 1997; Béniguel et al., 2004) and could make the evaluation of the IgG abnormalities in a population already exposed to environmental factors that have an impact on the reconstitution of the immune profile during ART difficult.

In conclusion it was found that in Malawian women receiving ART, the trend of IgG recovery is progressive but slow and is still incomplete after 24 months in terms of total IgG levels and proportions.

Considering the physiological importance of IgG acquisition through transplacental passage for infant health, the reduction of hypergammaglobulinemia in HIV-positive pregnant women should be monitored under the current Option B + approach to assess the benefits of the strategy in reducing the risk of infection in HIV-exposed infants.

Funding

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

References

Abudulai LN, Fernandez S, Corscadden K, Hunter M, Kirkham LA, Post JJ, et al. Chronic HIV-1 infection induces B-cell dysfunction that is incompletely resolved by long-term antiretroviral therapy. J Acquir Immune Defic Syndr 2016;71:381–9.

Abu-Raya B, Kollmann TR, Marchant A, MacGillivray DM. The immune system of HIV-exposed uninfected infants. Front Immunol 2016;7:383.

Amu S, Lavy-Shahaf G, Cagigi A, Hejdeman B, Nozza S, Lopalco L, et al. Frequency and phenotype of B cell subpopulations in young and aged HIV-1 infected patients receiving ART. Retrovirology 2014;11:76.

Babakhanyan A, Ekali GL, Dent A, Kazura J, Nguasong JT, Fodjo BAY, et al. Maternal human immunodeficiency virus-associated hypergammaglobulinemia reduces transplacental transfer of immunoglobulin G to Plasmodium falciparum antigens in Cameroonian neonates. Open Forum Infect Dis 2016;3:ofw092.

Baroncelli S, Galluzzo CM, Liotta G, Andreotti M, Mancinelli S, Mphwere R, et al. Deficit of IgG2 in HIV-positive pregnant women is responsible of inadequate IgG2 levels in their HIV-uninfected children in Malawi. Med Microbiol Immunol 2018;207:175–82.

Béniguel L, Bégaud E, Cognasse F, Gabrié P, Mbolidi CD, Sabido O, et al. Identification of germinal center B cells in blood from HIV-infected drug-naive individuals in Central Africa. Clin Dev Immunol 2004;11:23–7.

Bohlius J, Schmidlin K, Costagliola D, Fatkenheuer G, May M, Caro-Murillo AM, et al. Collaboration of Observational HIV Epidemiological Research Europe (COHERE) Study Group. Incidence and risk factors of HIV-related non-Hodgkin's lymphoma in the era of combination antiretroviral therapy: a European multicohort study. Antivir Ther 2009;14:1065–74.

Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med 2006;12:1365–71.

Brennan AT, Bonawitz R, Gill CJ, Thea DM, Kleinman M, Useem J, et al. A meta-analysis assessing all-cause mortality in HIV-exposed uninfected compared with HIV-unexposed uninfected infants and children. AIDS 2016;30:2351–60.

Cagigi A, Nilsson A, De Milito A, Chiodi F. B cell immunopathology during HIV-1 infection: lessons to learn for HIV-1 vaccine design. Vaccine 2008;26:3016–25.

Cagigi A, Nilsson A, Pensieroso S, Chiodi F. Dysfunctional B-cell responses during HIV-1 infection: implication for influenza vaccination and highly active antiretroviral therapy. Lancet Infect Dis 2010;10:499–503.

Chong Y, Ikematsu H, Kikuchi K, Yamamoto M, Murata M, Nishimura M, et al. Selective CD27+(memory) B cell reduction and characteristic B cell alteration in drug-naive and HAART-treated HIV type 1-infected patients. AIDS Res Hum Retroviruses 2004;20:219–26.

Cumberland P, Shulman CE, Maple PA, Bulmer JN, Dorman EK, Kawuondo K, et al. Maternal HIV infection and placental malaria reduce transplacental antibody transfer and tetanus antibody levels in newborns in Kenya. J Infect Dis 2007;196:550–7.

de Moraes-Pinto MI, Verhoeff F, Chimsuku L, Milligan PJ, Wesumperuma L, Broadhead RL, et al. Placental antibody transfer: influence of maternal HIV infection and placental malaria. Arch Dis Child 1998;79:F202–5.

De Milito A, Nilsson A, Titanji K, Thorstensson R, Reizenstein E, Narita M, et al. Mechanisms of hypergammaglobulinemia and impaired antigen-specific humoral immunity in HIV-1 infection. Blood 2004;103:2180–6.

Dobaño C, Santano R, Vidal M, Jiménez A, Jairoce C, Ubillos I, et al. Differential patterns of IgG subclass responses to Plasmodium falciparum antigens in relation to malaria protection and RTS,S vaccination. Front Immunol 2019;10:439.

D'Orsogna LG, Krueger RG, Elizabeth J, McKinnon EJ, Martyn A, French MA. Circulating memory B-cell subpopulations are affected differently by HIV infection and antiretroviral therapy. AIDS 2007;21:1747–52.

Giuliano M, Andreotti M, Liotta G, Jere H, Sagno JB, Maulidi M, et al. Maternal antiretroviral therapy for the prevention of mother-to-child transmission of HIV in Malawi: maternal and infant outcomes two years after delivery. PLoS One 2013;8:e68950.

Hentrich M, Barta S. HIV—associated hematological malignancies. Cham: Springer International Publishing; 2016 Holder Springer International Publishing Switzerland eBook.

Hu Z, Luo Z, Wan Z, Wu H, Li W, Zhang T, et al. HIV-associated memory B cell perturbations. Vaccine 2015;33:2524–9.

Kawano Y, Noma T, Yata J. Regulation of human IgG subclass production by cytokines. IFN-gamma and IL-6 act antagonistically in the induction of human IgG1 but additively in the induction of IgG2. J Immunol 1994;153:4948–58.

Longwe H, Gordon S, Malamba R, French N. Charaterising B cell numbers and memory B cells in HIV infected and uninfected Malawian adults. BMC Infect Dis 2010;10:280.

Malaspina A, Moir S, Kottilil S, Hallahan CW, Ehler LA, Liu S, et al. Deleterious effect of HIV-1 plasma viremia on B cell costimulatory function. J Immunol 2003;170:5965–72.

McGowan JP, Shah SS, Small CB, Klein RS, Schnipper SM, Chang CJ, et al. Relationship of serum immunoglobulin and IgG subclass levels to race, ethnicity and behavioral characteristics in HIV infection. Med Sci Monit 2006;12:CR11–6.

Mehraj V, Ramendra R, Isnard S, Dupuy FP, Lebouché B, Costiniuk C, et al. CXCL13 as a biomarker of immune activation during early and chronic HIV infection. Front Immunol 2019;10:289.

Moir S, Fauci AS. Pathogenic mechanisms of B-lymphocyte dysfunction in HIV disease. J Allergy Clin Immunol 2008;122:12–9.

Moir S, Buckner CM, Ho J, Wang W, Chen J, Waldner AJ, et al. B cells in early and chronic HIV infection: evidence for preservation of immune function associated with early initiation of antiretroviral therapy. Blood 2010;116:5571–9.

Moir S, Fauci AS. B-cell responses to HIV infection. Immunol Rev 2017;275:33–48.

National Malaria Control Programme (NMCP) and ICF. Malawi malaria indicator survey 2017. Lilongwe, Malawi, and Rockville, Maryland, USA: NMCP and ICF; 2018 At: https://dhsprogram.com/pubs/pdf/MIS28/MIS28.pdf. [Accessed May 2019].

Notermans DW, de Jong JJ, Goudsmit J, Bakker M, Roos MT, Nijholt L, et al. Potent antiretroviral therapy initiates normalization of hypergammaglobulinemia and a decline in HIV type 1-specific antibody responses. AIDS Res Hum Retroviruses 2001;17:1003–8.

Palmeira P, Quinello C, Silveira-Lessa AL, Zago CA, Carneiro-Sampaio M. IgG placental transfer in healthy and pathological pregnancies. Clin Dev Immunol 2012;2012:985646.

Pensieroso S, Cagigi A, Palma P, Nilsson A, Capponi C, Freda E, et al. Timing of HAART defines the integrity of memory B cells and the longevity of humoral responses in HIV-1 vertically-infected children. Proc Natl Acad Sci U S A 2009;106:7939–44.

Pensieroso S, Galli L, Nozza S, Ruffin N, Castagna A, Tambussi G, et al. B-cell subset alterations and correlated factors in HIV-1 infection. AIDS 2013;15:27:1209–17.

Pieters H, Brand CE, Badenhorst PN, Hendricks ML. Immunoglobulin G sub-class concentrations in South African adults: ethnic differences and reference ranges. Br J Biomed Sci 1997;54:104–9.

Pogliaghi M, Ripa M, Pensieroso S, Tolazzi M, Chiappetta S, Nozza S, et al. Beneficial effects of cART Initiated during primary and chronic HIV-1 infection on immunoglobulin-expression of memory B-cell subsets. PLoS One 2015;10:e0140435.

Puissant-Lubrano B, Peres M, Apoil P, Congy-Jolivet N, Roubinet F, Blancher A. Immunoglobulin IgA, IgD, IgG, IgM and IgG subclass reference values in adults. Clin Chem Lab Med 2015;53:e359–61.

Raux M, Finkielsztejn L, Salmon-Céron D, Bouchez H, Excler JL, Dulioust E, et al. IgG subclass distribution in serum and various mucosal fluids of HIV type 1-infected subjects. AIDS Res Hum Retroviruses 2000;16:583–94.

Redgrave BE, Stone SF, French MAH, Krueger R, James IR, Price P. The effect of combination antiretroviral therapy on CD5 B cells, B-cell activation and hypergammaglobulinaemia in HIV-1-infected patients. HIV Med 2005;6:307–12.

Regidor DL, Detels D, Breen EC, Widney DP, Jacobson LP, Palella F, et al. Effect of highly active antiretroviral therapy on biomarkers of B-lymphocyte activation and inflammation. AIDS 2011;25:303–14.

Rouhani M, Zakeri S, Mehrizi AA, Djadid ND. Comparative analysis of the profiles of IgG subclass-specific responses to Plasmodium falciparum apical membrane antigen-1 and merozoite surface protein-1 in naturally exposed individuals living in malaria hypoendemic settings. Iran Malar J 2015;14:58.

Scopel KKG, Fontes CJF, Ferreira MU, Braga EM. Factors associated with immunoglobulin G subclass polarization in naturally acquired antibodies to Plasmodium falciparum merozoite surface proteins: a cross-sectional survey in Brazilian Amazonia. Clin Vaccine Immunol 2006;13:810–3.

Serpa J, Haque D, Valayam J, Breaux K, Rodriguez-Barradas MC. Effect of combination antiretroviral treatment on total protein and calculated globulin levels among HIV-infected patients. Int J Infect Dis 2010;14S:e41–4.

Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. Proc Biol Sci 2015;282:1821.

Tangye SG, Ferguson A, Avery DT, Ma CS, Hodgkin PD. Isotype switching by human B cells is division-associated and regulated by cytokines. J Immunol 2002;169:4298–306.

Tanko F, Soares AP, Muller TL, Garrett NJ, Samsunder N, Karim QA, et al. Effect of antiretroviral therapy on the memory and activation profiles of B cells in HIV-infected African women. J Immunol 2017;198:1220–8.

Titanji K, De Milito A, Cagigi A, Thorstensson R, Grutzmeier S, Atlas A, et al. Loss of memory B cells impairs maintenance of long-term serologic memory during HIV-1 infection. Blood 2006;108:1580–7.

Joint United Nations HIV/AIDS Programme. Ending AIDS progress towards the 90-90-90 targets—global AIDS update 2017. Geneva: UNAIDS; 2017 Available online at: http://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf. [Accessed May 2019].

Vidarsson G, Dekkers G, Rispens T. IgG subclasses and allotypes: from structure to effector functions. Front Immunol 2014;5:520.