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Haematological effects of zidovudine prophylaxis in newborn infants with and without prenatal exposure to zidovudine

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6 **Haematological effects of zidovudine prophylaxis in newborn infants with and without**
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8 **prenatal exposure to zidovudine**
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25 Running head: Haematological effects of postnatal ZDV
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ABSTRACT

Postnatal prophylaxis with oral zidovudine (ZDV) is associated with haematological effects.

However, it is still unknown whether selection of non-ZDV based regimens in pregnancy may reduce haematological toxicity associated with postnatal ZDV prophylaxis.

The aim of this study was to define the haematological effects of zidovudine prophylaxis in newborns with and without prenatal exposure to ZDV. Sixty-five newborns from mothers infected with HIV who, during pregnancy, received HAART regimens with (n:44) and without (n: 21) ZDV were evaluated. Virological and haematological data were compared at birth and at four weeks and six months of life. Newborns with prenatal ZDV exposure had significantly worse haematological values at birth, with lower levels of haemoglobin (14.3 vs. 16.2 g/dl, $p=0.001$), red blood cell count (3.45 vs. 4.48×10^6 cells/mm³, $p<0.001$), and haematocrit (41.0 vs. 46.8%, $p<0.001$), and higher values of mean corpuscular volume (119 vs. 103 fl, $p<0.001$). The start of ZDV prophylaxis determined significantly greater adverse haematological changes in newborns without prenatal ZDV exposure, and at four weeks and six months of life the two groups had substantially identical haematological values.

The selection of non-ZDV based regimens in pregnancy does not reduce the final haematological effects of postnatal ZDV at four weeks and at six months of life. However, two distinct pathways may be observed: newborns exposed prenatally to ZDV have worse haematological values at birth, while newborns without prenatal ZDV exposure have particularly marked postnatal effects. The distinct effects of these two pathways should be considered.

Keywords: HIV; antiretroviral therapy; paediatrics anaemia; zidovudine

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INTRODUCTION

Both HIV infection and use of zidovudine (ZDV) may induce negative haematological effects, such as anaemia and macrocytosis (Sullivan et al., 1998; Eyer-Silva et al., 2001; Moyle, 2002; Romanelli et al., 2002). These haematological abnormalities may have particular relevance in pregnancy. Although current treatment guidelines recommend the use of zidovudine (Perinatal HIV Guidelines Working Group, 2009), perinatal ZDV exposure has been associated with transient maternal and neonatal haematological effects (Bunders et al., 2005; El Beitune et al., 2006; Pacheco et al., 2006; Briand et al., 2007; Feiterna-Sperling et al., 2007). The additional six-week postnatal course of ZDV, also recommended by treatment guidelines (Perinatal HIV Guidelines Working Group, 2009), can represent an important additional factor for the development of anaemia in newborns (Mandelbrot et al., 2001; Feiterna-Sperling et al., 2007; Bae et al., 2008), and small but durable haematological effects may be observed until 18 months of age (Le Chenadec et al., 2003).

The increasing use of non-thymidine analogues as the basis of antiretroviral therapy (ARV) regimens in people with HIV, favoured by the better side-effects of these drugs, has led to increased use of these drugs in pregnant women with HIV (Baroncelli et al., 2009). As a consequence, an increasing number of newborns of mothers infected with HIV have no prenatal exposure to ZDV, and are only exposed to postnatal ZDV prophylaxis. Within this situation, it is not yet known to what extent prenatal ZDV exposure increases the severity of the adverse haematological effects of postnatal ZDV prophylaxis, or whether children without prenatal ZDV exposure are more protected against the significant haematological toxicity of postnatal ZDV. The aim of this study was to investigate these issues by comparing haematological results at birth, at 4 weeks and at 6 months of life in two groups of newborns, whose mothers had received ARV regimens with and without zidovudine during pregnancy.

MATERIALS AND METHODS

Study population

The study population included singleton newborns of mothers infected with HIV who, during pregnancy, had received highly active antiretroviral therapy (HAART), defined by two nucleoside reverse transcriptase inhibitors (NRTI) plus either a protease inhibitor (PI) or nevirapine. All the pregnant women in this study were followed at the same clinical site (A. Gemelli Polyclinic, Catholic University, Rome), as part of the National Surveillance Program on Antiretroviral Treatment in Pregnancy, an ongoing nationwide study on pregnant women with HIV established in Italy in 2001 (Florida et al., 2006). The study, that received approval by the competent ethic committee, is observational, and the regimens are selected by the treating physician. Each patient provided informed consent for the collection of data and samples. All full-term newborns (gestational age >37 weeks) with available data on maternal HAART during pregnancy, birth weight, APGAR score, HIV status and haematological values were considered.

Study design

All the mothers were followed regularly during pregnancy, and received at least ten weeks of HAART during pregnancy. Clinical and virological evaluations were performed at each trimester, and delivery was scheduled by Caesarean section at week 38. All mothers received intravenous ZDV during delivery, and neonates were formula-fed. Neonatal prophylaxis with oral ZDV (2 mg/kg every 6 hours) (Perinatal HIV Guidelines Working Group, 2009) was started within 12 hours of birth. According to the characteristics of prenatal exposure, two groups were considered and compared: newborns of mothers who received ZDV-based HAART regimens in pregnancy (group A) and newborns of mothers who received ZDV-free HAART regimens (group B). Soon after birth, at one and at six months of life, a complete virological and haematological evaluation was performed. Neonatal anaemia was defined according to the Paediatric AIDS Clinical Trials Group

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3 (PACTG) toxicity tables (Table for Grading the Severity of Adult and Paediatric Adverse Events,
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5 2004).
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10 *Statistical analysis*
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12 Demographic data were summarised in descriptive statistics. Categorical data were compared using
13 the χ^2 test or Fisher test, as appropriate. Quantitative data were compared by the T test for
14 independent samples or by the T-test for paired samples. Assumption of normality was tested by
15 review of plots and by the Kolgomorov-Smirnov test. All the analyses were performed using the
16 SPSS software, version 17.0. (SPSS Inc., Chicago, Illinois, US).
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RESULTS

Main maternal and neonatal outcomes.

Overall, 65 mothers and their newborns were studied. Their general characteristics are reported in Table 1. At the end of pregnancy, mothers from the two groups had similar levels of HIV-RNA and CD4 cells. The maternal haemoglobin (Hb) levels of the mothers in the two groups were also similar (group A: 11.3 ± 1.2 g/dl; group B: 11.2 ± 1.4 g/dl, $p=0.885$), with no differences in the proportion of women with haemoglobin levels below 11.0 g/dl at 36 weeks (Table 1). No differences were observed in the main pregnancy outcomes and in gender, birth weight, and APGAR scores of the newborns, either (Table 1). All the newborns received daily oral zidovudine from birth to 6 weeks. None of the infants were positive for HIV-1 by PCR at birth or during follow-up.

Haematological values at birth.

The analysis of haematological data at birth revealed important differences between the two groups. Compared to newborns without prenatal exposure to ZDV, newborns exposed prenatally to ZDV had significantly lower levels of haemoglobin (14.3 vs. 16.2 g/dl, $p=0.001$), haematocrit (HCT: 41.0 vs. 46.3%, $p<0.001$), red blood cell count (RBC: 3.44 vs. 4.47×10^6 cells/mm³, $p<0.001$), and significantly higher mean corpuscular volume (MCV: 119.3 vs. 103.1 fl, $p<0.001$) and mean corpuscular haemoglobin (MCH: 41.6 vs. 36.6 pg, $p<0.001$) levels. A 17.1% of the newborns exposed prenatally to ZDV had abnormal haemoglobin levels (<13.0 g/dl, PACTG toxicity grading (Table for Grading the Severity of Adult and Paediatric Adverse Events, 2004), while all the newborns without prenatal ZDV exposure had haemoglobin levels above this threshold. No differences between the two groups were observed in platelets, white blood count (WBC) or the absolute neutrophil count (Table 2).

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3 *Haematological values at 4 weeks of life.*

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5 All the haematological differences noted at birth between the two groups disappeared at one month
6 of life, but different trends in haematological values were observed for the two groups, as reported
7 in Figure 1 and Table 2.

8
9 Compared to newborns with prenatal exposure to ZDV, those without prenatal exposure to ZDV
10 showed significantly lower values of haemoglobin, RBCs and HCT than those at birth, and
11 significantly lower reductions in the mean corpuscular volume and the mean corpuscular
12 haemoglobin (Table 3). The two groups had similar haemoglobin levels at 4 weeks of life (11.0 vs.
13 10.6 g/dl, Table 2). In group B 70.6% of neonates showed heamoglobin levels below 11.0 g/dl,
14 compared to 46.5% in group A.

15
16 In the first 4 weeks of life newborns exposed prenatally exposed to ZDV (group A) showed a mild
17 increase in RBCs compared to values at birth (+ 0.14 cells $\times 10^6/\text{mm}^3$, +3.9 %). In contrast,
18 newborns unexposed prenatally to ZDV (group B) had a marked decrease in RBC (-1.19 cells
19 $\times 10^6/\text{mm}^3$, -25.9%) ($p < 0.001$) (Table 3). A different pattern between the two groups was also
20 observed for MCV, that showed a marked decrement (-22.4%) among infants in group A,
21 significantly greater than that observed in group B babies (-9.1 %, $p < 0.001$). The same pattern
22 observed for MCV was also observed for MCH, with a significant difference in postnatal changes
23 between the two groups ($p < 0.001$). No significant differences were noted for mean corpuscular
24 haemoglobin concentration (MCHC) changes (Table 3). No differences between groups were
25 observed for platelets, white blood cell counts and absolute neutrophil count (Table 2).

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53 *Haematological values at 6 months of life.*

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55 At 6 months of life and about 16 weeks after interruption of ZDV haematological differences were
56 not observed between the two groups (Table 2), with similar values for haemoglobin, RBCs, and
57 MCV (Figure 1).

DISCUSSION

The present study describes in detail the haematological status in the first weeks of life in newborns from women receiving ZDV-free regimens in pregnancy, which represent a growing proportion of newborns of women with HIV. The main finding of this study is that, in newborns receiving postnatal ZDV prophylaxis, prenatal ZDV exposure has no additional haematological effects in the first months of life, with similar haematological values at four weeks and at six months of life irrespective of the use of ZDV-free regimens or ZDV-based HAART regimens during pregnancy.

However, newborns of women receiving ZDV-free regimens during pregnancy have a clearly distinct haematological pattern at birth and develop significantly different postnatal changes following the start of ZDV postnatal prophylaxis. These infants, compared to newborns with prenatal ZDV exposure, had better RBC, haemoglobin, MCV and MCH levels at birth, confirming the significant haematological effects of *in utero* exposure to zidovudine. With respect to findings in a healthy population (Christensen et al., 2009), newborns of women receiving ZDV-free regimens in pregnancy had slightly lower Hb levels. This finding could be consistent with mild prenatal haematological effects of other NRTIs, antiretroviral treatment in general, or, possibly, maternal HIV infection. A possible additional haematological effect of lamivudine, described by other investigators (Mandelbrot et al 2001; Feiterna-Sperling et al., 2007), could not be evaluated because this drug was present in almost all maternal regimens. The potential role of prenatal exposure to PI or nevirapine was also not assessed, but available data and pharmacokinetic considerations suggest that these drugs are unlikely to interfere with haematological values at birth (Marzolini et al., 2002; Feiterna-Sperling et al., 2007).

In the first weeks of life, compared to newborns with exposure *in utero* to ZDV, postnatal zidovudine prophylaxis induced significantly greater adverse haematological changes in neonates without antenatal ZDV exposure. Significant toxicity changes developed in these newborns at only four weeks, suggesting a particular vulnerability of the newborn to the myelosuppressive effects of ZDV. In contrast with previous reports (Mandelbrot et al., 2001; Le Chenadec et al., 2003; Bunders

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3 et al., 2005), no significant effects of ZDV on platelets, white blood cell counts and absolute
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5 neutrophil counts were found.
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8 In terms of clinical relevance, these data indicate that irrespective of antenatal regimens, all
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10 newborns who receive postnatal ZDV prophylaxis have a similar haematological status at one and
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12 at six months of life, with a frequent occurrence of anaemia. This study showed that use of ZDV-
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14 free regimens in pregnancy does not protect the newborns against the development of significant
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16 postnatal haematological toxicity following the start of postnatal ZDV prophylaxis. Usually, such
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18 effects are not clinically serious and should not preclude *per se* ZDV use in newborns, which has
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20 shown important benefits. It is however important to note that premature infants were excluded
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22 from this study, and it is **not known** whether the marked postnatal changes associated with ZDV
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24 prophylaxis in newborns **not exposed previously to antiretroviral drugs** may have particular clinical
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26 relevance in the presence of prematurity, low birth weight, or other conditions at risk (including use
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28 of haemato toxic drugs, such as cotrimoxazole). Similarly, the significant prenatal effect of **the use**
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30 **of** maternal ZDV in reducing haemoglobin concentrations at birth should be considered when
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32 prescribing ZDV in pregnancy to mothers with clinical conditions potentially responsible for a
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34 reduced oxygen supply to the fetus.
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FIGURE LEGEND

Figure 1. Postnatal changes in haematological parameters in neonates receiving postnatal zidovudine (ZDV) prophylaxis. The 6 weeks of ZDV postnatal exposure are represented by the grey area.

- ◆ neonates with *in utero* exposure to ZDV (Group A);
- △ neonates with no *in utero* exposure to ZDV (Group B);

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Table 1. Characteristics of mothers at 36 weeks of pregnancy and newborns

	Prenatal ZDV (group A) (n:44)	No prenatal ZDV (group B) (n:21)	P value
<i>Mothers</i>			
Ethnicity (caucasian)	32 (71.1%)	19 (90.5%)	0.117
Haemoglobin <11 g/dl at week 36*	20 (45.5%)	11 (52.4%)	0.601
Detectable HIV-RNA at week 36 (n:35)	9 (22.0%)	3 (14.3%)	0.581
Maternal CD4 at week 36 (cells/mm ³) (n:35)	536 ± 268	571 ± 195	0.602
Use of PI-based HAART in pregnancy	36 (81.8%)	17 (85.0%)	0.754
Duration of HAART in pregnancy (weeks)	22.1 ± 9.6	31.9 ± 1.0	<0.001
<i>Newborns</i>			
Gender (male: n, %)	22 (51.2 %)	6 (31.6%)	0.153
Birthweight (g)	2877 ± 374	2960 ± 500	0.580
APGAR score	8.9 ± 0.8	8.7 ± 0.9	0.341

* Definition of anaemia according to WHO guidelines for pregnant women in third trimester (UNICEF Iron deficiency anaemia. 2001)

PI: protease inhibitors; NNRTI: non-nucleoside reverse transcriptase inhibitors

Treatment details:

- NRTI: all group A mothers received zidovudine plus lamivudine; in group B more than half regimens (12/21, 57.1%) included lamivudine: 3TC+ABC: n:3, 14.3%; 3TC+d4T: n:3, 14.3%; 3TC+TDF: n:6, 28.6% the remaining mother (9, 42.9%) received TDF+FTC.

- PI (overall rate of use: 83.1%) included: lopinavir/ritonavir (n: 34); nelfinavir (n: 9); atazanavir/ritonavir (n: 6); saquinavir/ritonavir (n: 4) and darunavir/ritonavir (n: 1).

- NNRTI included nevirapine only (n:11)

Table 2. Haematological data in newborns at birth, four weeks and six months of life.

Haematology, newborn	at birth			at 4 weeks of life			at 6 months of life		
	Prenatal	No prenatal	<i>P value</i>	Prenatal	No prenatal	<i>P value</i>	Prenatal	No prenatal	<i>P value</i>
	ZDV	ZDV		ZDV	ZDV		ZDV	ZDV	
Haemoglobin <13 (or 11 g/dl) [#]	7 (17.1%)	0 (0%)	0.089	20 (46.5%)	12 (70.6%)	0.092	5 (14.3%)	1 (9.1%)	1.000
Haemoglobin (g/dl)	14.3 ± 2.1	16.2 ± 1.5	0.001	11.0 ± 1.2	10.6 ± 1.4	0.193	12.3 ± 1.1	11.9 ± 0.4	0.070
RBC (10 ³ cells/mm ³)	3.45 ± 0.56	4.48 ± 0.41	<0.001	3.58 ± 0.82	3.31 ± 0.61	0.168	4.67 ± 0.54	4.47 ± 0.43	0.150
HCT (%)	41.0 ± 6.2	46.8 ± 4.0	<0.001	32.3 ± 3.9	30.7 ± 4.40	0.213	35.9 ± 3.4	34.6 ± 2.2	0.254
MCV (fl)	119 ± 7.58	103 ± 9.53	<0.001	92.5 ± 12.2	93.7 ± 7.0	0.716	77.9 ± 5.5	78.3 ± 5.3	0.835
MCH (pg)	41.6 ± 3.23	36.7 ± 3.49	<0.001	31.7 ± 4.4	32.1 ± 2.6	0.724	26.5 ± 1.9	27.7 ± 3.5	0.136
MCHC (g/dl)	34.6 ± 2.4	34.3 ± 3.19	0.152	34.2 ± 1.2	34.3 ± 1.2	0.795	33.8 ± 2.1	34.3 ± 1.2	0.407
PLT (10 ³ cells/mm ³)	326 ± 84.2	348 ± 100	0.377	506 ± 136	521 ± 202	0.740	454 ± 119	408 ± 180	0.333
WBC (10 ³ cells/mm ³)	14.1 ± 4.8	13.8 ± 6.2	0.871	10.5 ± 2.7	8.9 ± 2.0	0.029	11.1 ± 3.5	10.2 ± 2.9	0.453
ANC (10 ³ cells/mm ³)	8.26 ± 4.73	8.20 ± 5.01	0.964	2.38 ± 1.51	2.08 ± 0.65	0.434	2.72 ± 1.33	3.27 ± 1.07	0.221

[#] Definition of anemia at birth (<13.0g/dl) and at one and six months (<11.0) of life according to *PACTG criteria* (Table for Grading the Severity of Adult and Paediatric Adverse Events, 2004).

RBC: red blood cells; HCT: haematocrit; MCV: mean corpuscular volume; MCH: Mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; PLT: platelets; WBC: white blood cells; ANC: absolute neutrophil count.

Table 3. Postnatal changes in haematological variables between birth and 1 month of life in newborns with and without prenatal zidovudine exposure.

Haematological variable	Mean postnatal change (month 0 – month 1)		Mean difference between groups in postnatal changes	95% CI for the difference		p value	Percent change between birth and 1 month	
	Prenatal ZDV	No prenatal ZDV		Lower	Upper		Prenatal ZDV	No prenatal ZDV
	Haemoglobin (g/dl)	- 3.23	- 5.69	2.46	0.94	3.97	0.002	-23.0%
RBC ($\times 10^6/\text{mm}^3$)	+ 0.14	- 1.19	1.33	0.76	1.90	<0.001	+ 3.9%	- 25.9%
HCT (%)	- 8.7	- 15.6	6.96	2.73	11.2	0.002	- 21.2%	- 34.4%
MCV (fl)	- 26.8	- 7.4	-19.4	-26.7	-12.1	<0.001	- 22.4%	- 9.1%
MCH (pg)	- 9.90	- 4.39	-5.51	-8.03	-2.99	<0.001	- 16.4%	- 13.7%
MCHC (g/dl)	- 0.38	- 1.07	0.69	-0.89	2.28	0.311	- 1.1%	- 0.1%
PLT($\times 10^3/\text{mm}^3$)	+175	+184	-9.20	-103.7	85.2	0.846	+ 55.2%	+ 49.7%
WBC($\times 10^3/\text{mm}^3$)	-3.54	-5.77	2.28	-0.98	5.43	0.170	- 25.3%	- 35.7%
Neut ($\times 10^3/\text{mm}^3$)	-5.83	-6.84	1.00	-1.97	3.99	0.405	-71.0%	-74.3%

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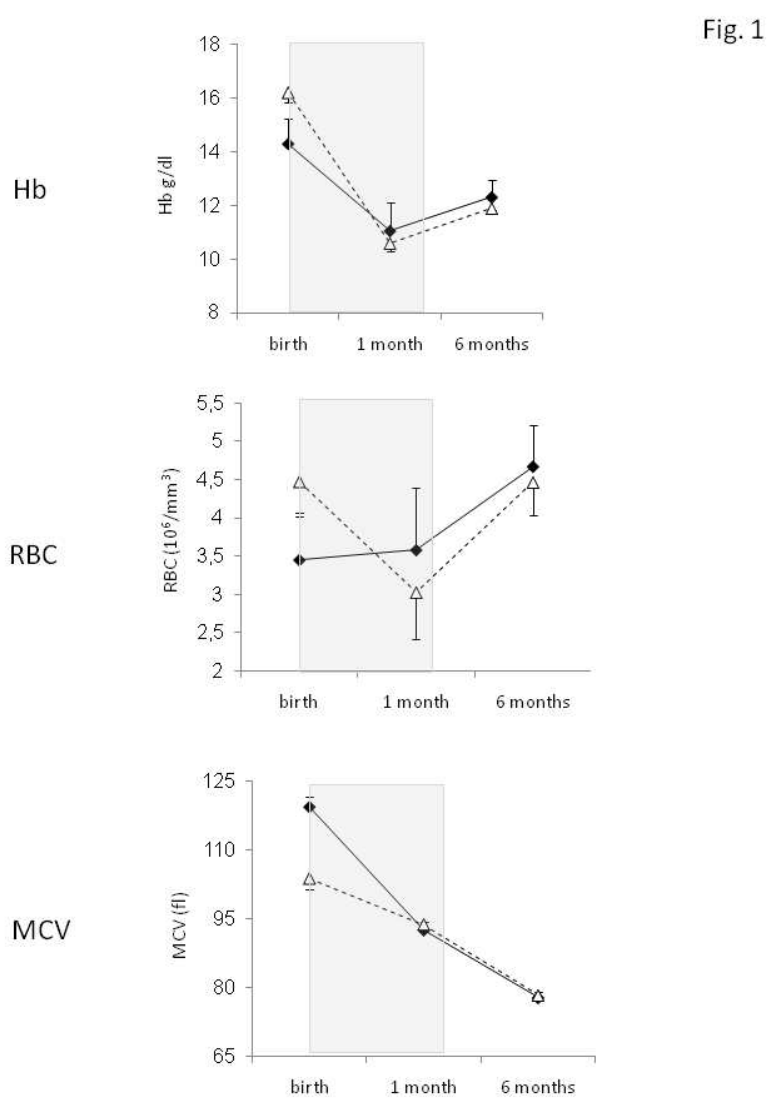


Figure 1
190x254mm (96 x 96 DPI)