Haematological manifestations of HIV infected and HIV exposed Infants at Harare Central Hospital, Zimbabwe.

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Abstract

Background: Prevention of mother to child transmission (PMTCT) programs have resulted in increased numbers of HIV exposed uninfected infants. However, these infants have higher morbidity and mortality rates like their HIV infected counterparts. Exposure to the maternal HIV infection or antiretroviral drugs in the uterus and by neonatal prophylaxis is thought to have an impact on the haematology of these infants. The aim of the study was to compare the haematological manifestations of HIV exposed uninfected infants with those of HIV infected infants as both groups are born to HIV positive mothers.

Methods: This was a prospective clinical and laboratory cross sectional study carried out at Harare Central Hospital in Zimbabwe from January to April 2017. Full blood counts were done on blood samples collected from HIV exposed uninfected and HIV infected infants between the age of 6 weeks and 2 years. Results were statistically analysed using SPSS version 20.

Results: A total of 150 infants were recruited into the study. Forty-one (27.3%) were HIV infected and 109 (72.7) were HIV exposed uninfected. Anaemia was the most common abnormality in both HIV infected (80.5%) and HIV exposed uninfected infants (75.6%).The most common type was microcytic hypochromic anaemia in HIV exposed uninfected infants and normocytic hypochromic anaemia in HIV infected infants. Leukopaenia, neutropaenia and thrombocytopaenia were 9.2% and 2.4%, 16.5% and 19.5% and 7.3% and 20% in HIV exposed uninfected and HIV infected infants respectively. Thrombocytosis was present in HIV exposed uninfected infants.

Conclusion: Abnormal haematological manifestations in HIV exposed uninfected infants were comparable to those of HIV infected infants. Anaemia was the common abnormality in the two groups of infants.

Keywords: *Anaemia, Cytopaenia, Haematological, HIV Exposed, HIV Infected, PMTCT*

Introduction

The number of new cases of human immunodeficiency virus (HIV) is decreasing, but the number of people living with HIV has been increasing globally. The decrease has been caused by the introduction of antiretroviral therapy (ART) which has significantly reduced mortality rate. Studies have shown that, although there is a global increase in HIV prevalence, there is a substantial decline in acquired immunodeficiency syndromes (AIDS) related deaths (*Maatens et al.,2014; Kharsany and Karin, 2016*). In addition to opportunistic infections, some syndromes manifest in haematological abnormalities such as anaemia, lymphoma and leukaemia. HIV is known to cause blood cancer (*Chinembiri et al., 2017*). A lot of studies have indicated changes in haematology associated with HIV infection. These changes are predominantly cytopaenia; anaemia, leukopaenia and thrombocytopaenia. Anaemia is responsible for the majority of deaths due to HIV/AIDS (*Santis et al, 2011; Ossitidima et al., 2016*). Changes in some haematological parameters with HIV infection may be useful in monitoring the health of people living with HIV/AIDS.

HIV infected infants are defined as those children who acquired infection from their HIV positive mothers. This is may be acquired transplacentally during pregnancy, during the process of labour and postnatally during breastfeeding. In children, HIV is one the major causes of infant mortality, mainly due to haematological abnormalities, specifically severe anaemia (*De Cock, 2000; Nkwo, 2012; Wiegert, 2014*).

HIV exposed uninfected (HEU) infants are defined as children who tested negative with the polymerase chain reaction (PCR) test who were born to HIV positive mothers. It has been found that these infants tend to exhibit poor health outcomes and have high morbidity and mortality rates comparable to that of infants who are HIV infected. These HEU infants, as a result, also pose serious public health challenges (*Filteau, 2009; Koye et al., 2013; Sugandhi et al., 2013; Evans et al., 2016*).

Although many children are born to HIV positive mothers each year globally, the number of those getting infected is declining. This is due to the introduction of the prevention of mother to child transmission (PMTCT) programmes to eradicate new childhood infections through vertical transmission. The PMTCT programmes provide ART to HIV positive pregnant mothers to prevent unborn infants from acquiring the infection. Follow ups on HEU infants has not been good enough as it is usually difficult to retain them for care and monitoring until the end of the exposure period (*Filteau, 2009; Koye et al., 2013; Sugandhi et al., 2013; Evans et al., 2016*)..

Haematological complications in HIV infection are very common and variable. They range from cytopaenia to thrombotic and bleeding tendencies, opportunistic infection of the bone marrow and malignancies. Anaemia (Hb<11 g/dl) is the most commonly encountered cytopaenia and is found in more than 90% of people living with HIV infection. Some cytopaenia are caused by ART and prophylactic antibiotic medications (*Opie, 2012*).

The above haematological manifestations were also found to be common in HEU infants with anaemia being the most common of the peripheral cytopaenia, especially during the late stages of the infection. Another study showed anaemia to be present in HEU infants, although it was less compared to HIV infected infants. Leukopaenia and thrombocytopaenia were also observed in the same study (*Aidetifa, 2013; Umar, 2015*). Similar findings were found in HEU infants whose results were compared to the haematological manifestations of those not infected and exposed. HEU infants on ART showed cytopaenia with anaemia being the most common. The same results were obtained even in follow up studies done at different intervals (*Bunders, 2005; Pacheco , 2006; Anyim, 2015*).

The introduction of the PMTCT programmes has seen a rapid increase in HEU infants. These children are faced with high morbidity and mortality as well (*Koye et al., 2013; Evans et al., 2016*). Studies associated with this programme have focused more on prevention of HIV and ART treatment than on the effects of these interventions on the health of HEU infants (*Filteau, 2009).* Currently, there is no sufficient haematology data to monitor the health of HIV and ART exposed infants. Many studies have been carried out globally on the haematology of HIV infection and very little is known about the haematology of HEU infants in Zimbabwe. The availability of this information will greatly assist in the monitoring and management of the health of this vulnerable population group.

Materials and Methods

A prospective clinical and laboratory based cross sectional study was carried out on HIV infected and exposed infants aged between 6 weeks and 2 years who were attending a Harare Central Hospital Opportunistic Infections (OI) Clinic and Paediatric Ward from January to April 2016.. Ethical approval was granted by the Harare Central Hospital Ethics Committee (HCHEC 101116/94) and the Joint Research Ethics Committee of the University of Zimbabwe College of Health Sciences and Parirenyatwa Group of Hospitals (JREC/418/16). Access to blood samples and testing was granted by the Harare Central Hospital Medical Director and Chief Medical Laboratory Scientist respectively.

The inclusion criteria were: infants who were HIV infected as confirmed by the PCR test and HEU infants between 6 week and 2 years of age; infants who were known to be free from preexisting abnormal haematological conditions. *The exclusion criteria* were: infants who had preexisting haematological conditions.

Demographic information was obtained from the patients' notes and record books from the OI clinic and Paediatric ward.

The sample size was determined using the Dobson's formula. Based on this formula, a minimum sample size for HEU was 73 and that for HIV infected was 38.

Fresh EDTA blood samples collected from the Harare Central Hospital OI clinic and Paediatric wards for routine full blood count (FBC) were used in the study. They were analyzed within two hours of collection using the Sysmex XT 4000i Haematology Analyzer (Sysmex Corporation, Kobe, Japan).

Results were collected and entered into Microsoft Excel for statistical analysis using the SPSS version 20. Descriptive analysis was done using means and standard deviations. Chi-square test was used to determine association between variables. P-values of less than 0.05 were considered to be significant. Graphs and tables were used to describe the results. Magnitudes of abnormalities were expressed as percentages of the prescribed totals.

Haematological abnormalities were described as those values that were outside the expected normal haematological reference ranges.

Results

A total of 150 blood samples were collected from the infants. One hundred and nine (72.7%) were from HEU infants and 41 (27.3%) were from HIV infected infants. More male infants were HEU than female infants and more female infants were HIV infected than male infants (*Table I*). Most of the HIV infected infants were in the 13-24 months age group, while the age distribution in the HEU infants was not markedly different (*Table II*).

Some haematological parameters showed statistically significant differences (<0.05) between HEU and HIV infected infants (*Table III)*.

About half of the measured haematological parameters were abnormal. Cytopaenia (*decreased cell populations*) was most common in HIV infected than in HEU infants. Anaemia was the most common cytopaenia and was present in 80.5% and 71.6 % of HIV infected and HEU infants respectively. However, the anaemia was mostly of the mild type (*Table IV*). This was followed by neutropaenia, thrombocytopaenia and lymphopaenia, in that order (*Figure 1*).

Morphologically, the predominant anaemia was microcytic hypochromic anaemia and this was most prevalent in HEU infants while HIV infected infants exhibited mostly normocytic hypochromic and microcytic normochromic anaemia. Macrocytic normochromic anaemia was the least prevalent in both infant groups (*Figure 2*).

Polycytosis (*increased cell populations*) was high in HEU than in HIV infected infants. Thrombocytosis was the most common of the polycytoses and it was higher in HEU infants. It was followed by lymphocytosis and leukocytosis which appeared to be higher in HEU than in HIV infected infants (*Figure 3*).

Table I: Gender Distribution of HEU and HIV infected infants

Status		Frequency n (%)
HIV exposed infants	Male	68 (62.4)
	Female	41 (37.6)
	Total	**109**
HIV infected infants	Male	20 (48.8)
	Female	21 (51.2)
	Total	**41**

Table II: Age Distribution of HEU and HIV infected infants

Status	Age group	Frequency n (%)
HEU Infants	2-12months	52 (47.7)
	13-24 months	57 (52.3)
	Total	109
HIV infected infants	2-12 months	10 (24.4)
	13-24 months	31 (75.6)
	Total	41

Table III: Mean Values and P-values of HEU and HIV infected infants.

Haematological Parameters	Normal Reference Range	Mean values (SD) HEU	Mean values (SD) HIV Infected	p-value
WBC [$\times 10^3/\mu$L]	4-11	12.55 (7.96)	9.04 (3.15)	0.007**
RBC [$\times 10^6/\mu L$]	3-5	4.35 (0.95)	3.73 (0.92)	0.0005***
Hb [g/dl]	11-18	9.98 (2.08)	9.06 (2.04)	0.017*
Hct [%]	37-54	32.22(6.08)	29.29 (6.35)	0.010*
MCV [fL]	75-96	75.73 (11.98)	79.82 (11.96)	0.064
MCH [pg]	27-32	23.78 (4.79)	24.66(3.79)	0.291
MCHC [%]	31-35	31.00 (2.39)	30.90 (2.00)	0.820
Platelets [$\times 10^3/\mu L$]	150-400	527.72 (315.56)	399.90 (245.58)	0.021*
Neutrophils [%]	35-76	38.43 (21.18)	41.11 (24.31)	0.506
Neutrophils [$\times 10^3/\mu L$]	1.8-7.24	4.93 (5.35)	3.82 (2.88)	0.210
Lymphocytes [%]	20-45	45.26 (19.23)	42.04 (18.82)	0.360
Lymphocytes [$\times 10^3/\mu L$]	1.5-3.5	5.21 (3.63)	3.81 (2.22)	0.022*
Monocytes [%]	2-10	9.03 (5.79)	13.26 (10.15)	0.002**
Monocytes [$\times 10^3/\mu L$]	0.2-1.07	1.07 (0.89)	1.12 (0.79)	0.742
Eosinophils [%]	0-5	1.03 (1.63)	1.49 (1.87)	0.144
Eosinophils [$\times 10^3/\mu L$]	0-0.4	0.14 (0.22)	0.13 (0.16)	0.941
Basophils [%]	0-2	1.34 (1.54)	1.26 (1.45)	0.774
Basophils [$\times 10^3/\mu L$]	0-0.1	0.13 (0.12)	0.11 (0.11)	0.262

Table IV: The Severity of anaemia in HEU and HIV infected infants.

Severity of anaemia	HIV Exposed Infants Frequency n (%)	HIV Infected Infants Frequency n (%)
Mild (Hb= 7- 11g g/dl)	71 (65.1)	27(65.9)
Moderate (Hb=5-7g/dl)	5 (4.6)	4 (9.8)
Severe (Hb<5 g/dl)	2 (1.8)	2 (4.9)

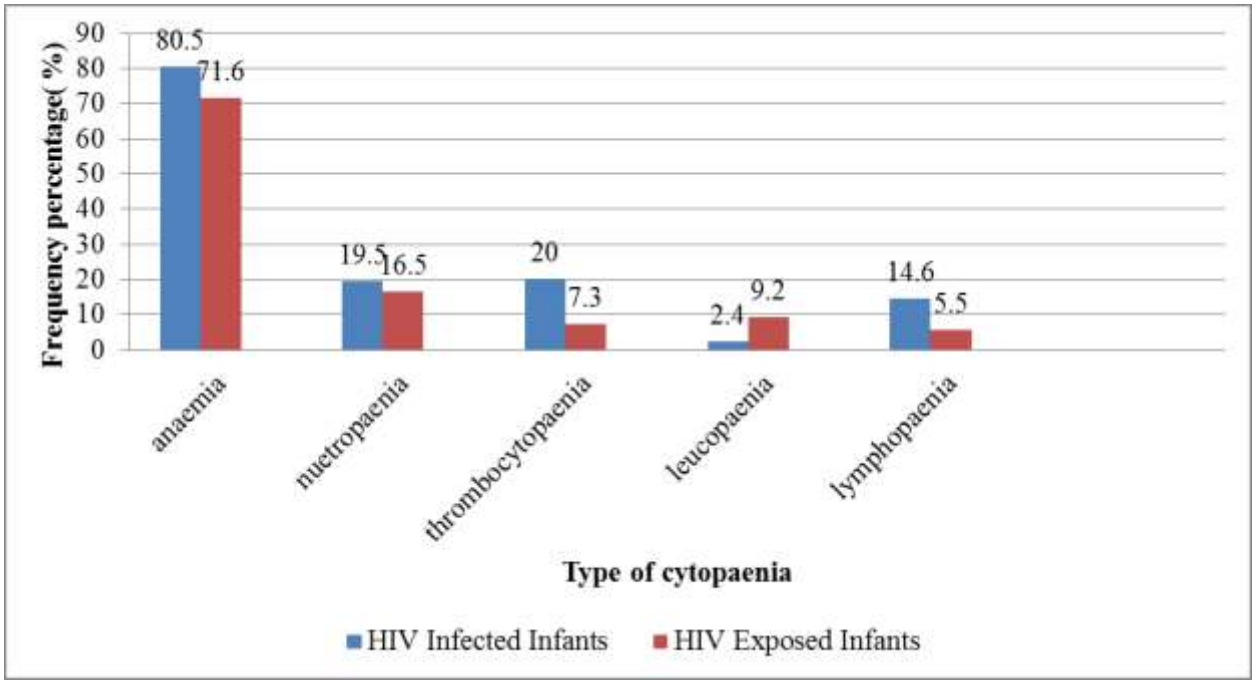

Fig 1: Distribution of cytopaenia in HEU and HIV infected infants.

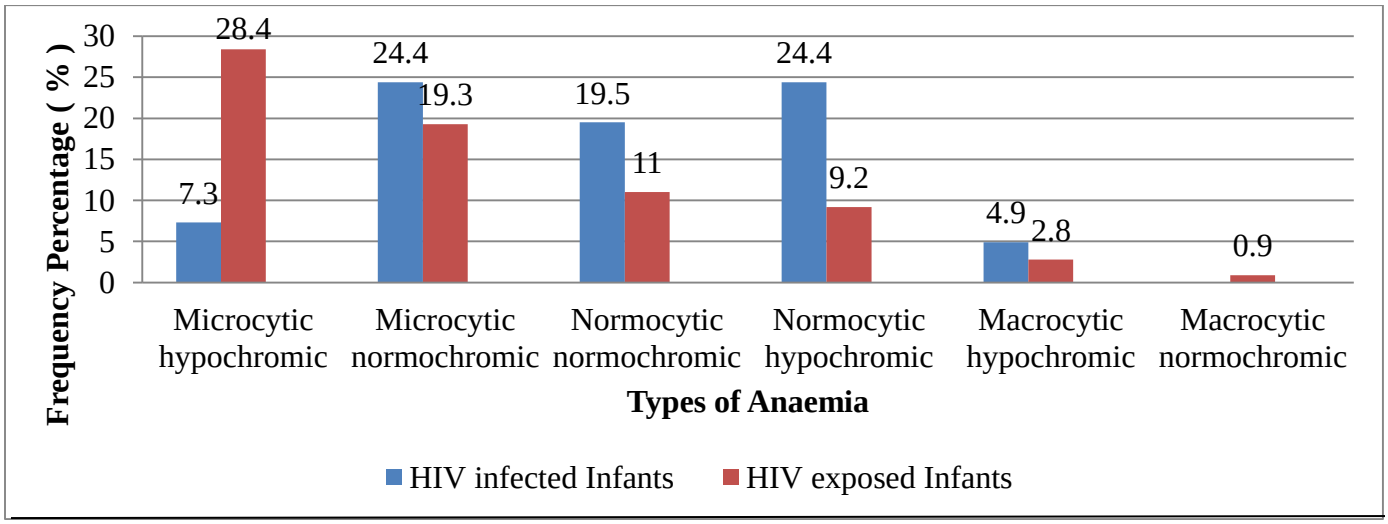

Fig 2: Morphological Distribution of Anaemia in HIV infected an HEU

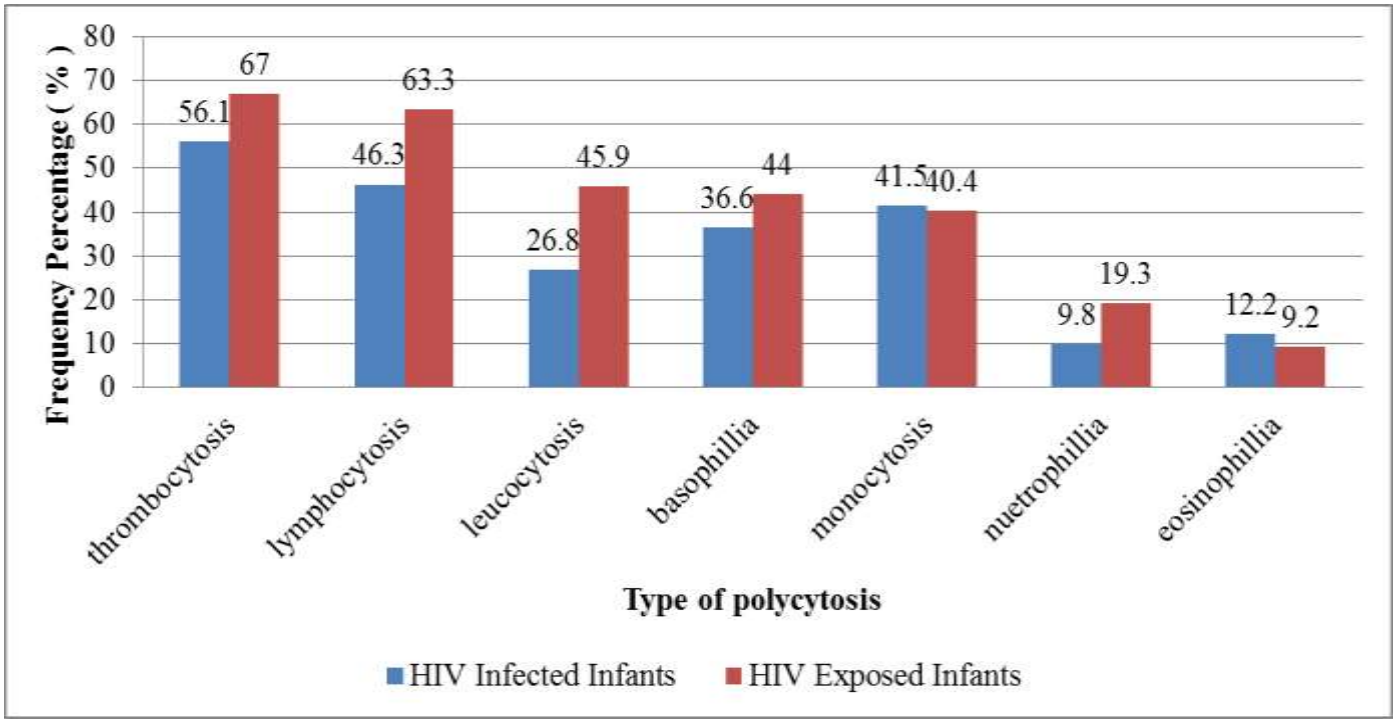

Fig 3: Distribution of Polycytosis in HIV infected and HEU infants.

Discussion and Conclusions

There were more HEU infants than HIV infected infants who participated in the study. This could be associated with more mothers participating in the PMTCT programmes which have significantly reduced vertical HIV transmissions. Previous studies have shown a significant decline in HIV prevalence in infants whose mothers participated in PMTCT programmes (*Okechukwu, 2008; Mirkuzie, 2012*). The other reason could have been fear and stigma associated with early infant HIV diagnosis by HIV positive mothers who did not want to disclose the HIV status of their infants. Lack of access to early infant diagnosis (EID) for HIV made it difficult to know the infant HIV status. Domestic violence by the male partners often discouraged HIV positive mothers from disclosing her status and that of the infant. The HIV infected infants status is not made available early enough for uptake of ART and PMTCT programmes and performance of some evaluation studies (*Odimegwu et al.,2013; Oladele et al., 2015; Hampanda et al.,2017*).

More male infants were HEU than their female counterparts and more female infants were HIV infected than their male counterparts. It is not clearly understood why there was this gender difference. However, it is thought female infants are susceptible to HIV infection in-utero and peripartum periods than their male counterparts. It is also thought that these gender differences could be associated with higher in-utero mortality rates of male HIV infected infants or to increased susceptibility of female infants to the infection (*Taha et al., 2005; Brahmbhatt et al., 2009*). Most of the HIV infected infants were in the 13-24 months age group. This could be associated with late or lack of adherence to participation in the PMTCT programmes, resulting in infants getting infected through vertical transmission. Prolonged exposure to breast milk was also found to cause infection to infants who were initially HIV negative. It has been found that

HIV transmission and mortality were very low in infants and HIV positive mothers who adhered to PMTCT programmes respectively (*Lussiana et al., 2012*).

Haematological parameters of HIV infected and HEU infants were variable. Some showed statistically significant differences between the two populations. Although the red blood cell count (RBC) and white blood cell count (WBC) were normal, anaemia (Hb<11 g/dl and Hct<37%) was present in HIV infected and HEU infants and the Hb and Hct were much lower in HIV infected infants than in HEU infants. The anaemia in HIV infected infants was consistent with several findings in studies on haematology of HIV infection. Some studies have seen no significant differences in severity of anaemia between the two populations (*Santis et al, 2011; George and Paul, 2015; Odhiambo et al., 2015; Ossitidima et al., 2016*). The origin of anaemia in HEU infants was probably associated with in utero exposure to maternal ART drugs. It is well documented that zidovudine causes bone marrow damage and dysplasia which result in anaemia and other haematological abnormalities due ineffective blood production (*Aupibul et al., 2008; Agrawal et al., 2010*). The statistical difference in platelet count was caused by increased count in HEU infants. This finding was fairly common and no previous studies have come up with reasons why this is the case. However, a study on the pathology of children born to HIV positive mothers has indicated that close to a quarter of HEU infants had thrombocytosis (*Roca et al., 2009*).

Cytopaenia was the most common haematological abnormality and anaemia was the most prominent cytopaenia, followed by neutropaenia. Haematology of HIV infection is characterized by this feature, according to several previous findings. These findings could be associated with viral and/or drug induced bone marrow damage in both HIV infected infants and HEU infants. In addition, cotrimoxazole prophylaxis was found to be associated with severe neutropaenia. HEU infants are often on cotrimoxazole prophylaxis (*Feiterna-Sperling et al., 2007; Hoffbrand and Moss, 2011; Dryden-Peterson et al., 2013*). Although the prevalence of anaemia was very high in the two populations, it was mostly of mild form. Mild anaemia, leukocytosis, lymphocytosis and thrombocytosis are expected as haematological indications of improved quality of life associated with antiretroviral drug uptake. It is important to note that anaemia remains the major contributing factor of the morbidity and mortality in HIV infected and HEU infants. Thrombocytosis could be a major risk factor for thrombosis in these infants. On the other hand, neutropaenia would render them very susceptible to severe infections. However, some studies have shown that although thrombocytosis was present in HEU it was not associated with any complications (*Feiterna-Sperling et al., 2007*).

Morphologically, the anaemia was mostly microcytic hypochromic, microcytic normochromic and normocytic hypochromic with a mean corpuscular volume that was low (<80fL). These were typical manifestations of iron deficiency. Therefore, it also can be argued that anaemia in HIV infected and HEU infants could have been also caused by iron deficiency during pregnancy or could be lack of iron in infant food (*Scholl, 2005*).

It can be concluded that haematological features in both HIV infected and HEU infants were markedly abnormal. Cytopaenia were the most common abnormalities lead by anaemia. However, the anaemia was largely of mild type. Based on morphological classification, a large number of HEU infants exhibited apparent iron deficiency anaemia.

It is recommended that HEU infants should be given the same medical attention that is given to their HIV infected counterparts, rather than making assumptions that they are ‘healthy because they were only exposed to HIV and not infected’. The PMTCT programmes must be scaled up to reduce vertical HIV transmissions in infants. Identification and care of HEU infants must be

done early enough to prevent perinatal infections (*Krist and Crawford-Faucher, 2002*). At the same time, there should be programmes in place to monitor the health of HEU infants and these should include evaluation of their haematology. Prophylactic cotrimoxazole given to prevent opportunistic infections must also be carefully monitored to reduce drug-induced neutropaenia. Iron supplements may need to be considered for both HIV infected and HEU infants to prevent iron deficiency anaemia.

The major limitation of the study was the small number of HIV infected infants who participated. The other limitation was the lack of information on the type of antiretroviral/ medication both groups of infants were taking.

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