

## TITLE PAGE

### Who gets severe gynaecomastia among HIV-infected children in the UK and Ireland?

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BRIEF REPORT TO PIDJ (max 1500 words, 10 refs, 1 figure or table)

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**Running head:** Gynaecomastia in HIV-infected children in UK/Ireland

## **Who gets severe gynaecomastia among HIV-infected children in the UK and Ireland?**

### **UNSTRUCTURED ABSTRACT**

There are few data on gynaecomastia in HIV-infected children. Within the UK/Ireland's national cohort, 56/1,873 (3%) HIV-infected children had gynaecomastia, of which 10 (0.5%) were severe. All 10 had received antiretroviral therapy for median 27.5 [21,42] months. 4/10 had received efavirenz, 7/10 and 6/10 stavudine and/or didanosine respectively. Five were non-reversible, despite changing ART, and required breast reduction surgery.

## **Who gets severe gynaecomastia among HIV-infected children in the UK and Ireland?**

### **Background**

Gynaecomastia has been described in HIV-infected adults taking antiretroviral therapy (ART) and has been linked to didanosine (ddI), efavirenz (EFV) and protease inhibitors (PI) [1-4], but very few cases have been described in HIV infected children [5-8]. We explored the frequency, aetiology and management of severe gynaecomastia in children with perinatal HIV in the UK and Ireland's national Collaborative HIV Paediatric Study (CHIPS) cohort.

### **Methods**

Details of the CHIPS cohort have been published previously [9]. Cases of gynaecomastia were identified from the CHIPS dataset up to April 2014, and additional case note review was undertaken to gather additional information. Severity of gynaecomastia was defined as mild (minor breast enlargement, no skin redundancy) moderate (moderate breast enlargement, minor skin redundancy) or severe (in males, marked breast enlargement, major skin redundancy (resembles female breast), in females excessive breast hypertrophy interfering with everyday activities). Descriptive statistics were calculated using Stata 13 (StataCorp, College Station, Texas).

### **Results**

Of 1,873 children ever in CHIPS, 52% (976) were female, 77% (1,452) were black African, and the median age at last follow-up was 15 [interquartile range, IQR 11, 17] years. A total of 56 (3%) had gynaecomastia, reported as mild (25), moderate (23) or severe (10). Of the 10 severe cases, 9 were male (Table 1). At onset the median age of severe cases was 13.5 [12, 14] years. All were on ART, and had been on their current regimen for a median of 27.5 [21, 42] months and on any ART regimen for 60.5 [31, 88] months. At time of report, 5 were on NNRTI-based regimens (EFV 4, nevirapine 1) and 5 PI-based (ritonavir-boosted lopinavir 3, nelfinavir (NVF) 2). Current NRTI backbones included

lamivudine (3TC) (6), abacavir (ABC) (4), stavudine (d4T) (4), ddl (6) and tenofovir (2). All 10 had previous or current exposure to d4T, ddl and/or EFV (7 d4T for a median of 42 [21, 74] months, 7 ddl for 21 [15, 22] months, 4 EFV for 29 [19, 39] months). 9/10 young people had a body mass index <25 (healthy/ underweight) and 6 had lipodystrophy at other sites (5/6 had exposure to d4T; ¼ to EFV). 6 patients switched ART regimens (3 patients subsequently stopped ART) with complete resolution reported within 2 years. 5 patients required breast reduction surgery and 1 was considering surgery at time of last follow up. One patient transferred to adult services and their outcome is unknown.

## **Discussion**

Mild to moderate gynaecomastia was relatively common in our cohort. Severe cases occurred in 1 in 200 children and were more likely in males, which may reflect difficulties in distinguishing normal pubertal development and/or obesity from pathological breast hypertrophy in girls. Only 2 severe cases occurred before age 12 years (both on stavudine and reversed with change of ART). Thus our findings support other reports that pre-pubertal gynaecomastia is rare, for example no cases were seen in the CHAPAS 3 trial in which 478 children aged under 13 years, 33% on d4T were followed for a median 2.3 years [10]. 3 children (aged 12, 12 and 15 years) in the ARROW trial of 1206 children (median age 6 [2 – 9] years, 37% on EFV; none on d4T- based ART) changed regimen due to lipodystrophy/gynaecomastia during 5 years of follow up [11].

Within our cohort initial management of gynaecomastia varied from immediate change of ART regimen to differing periods of observation, most of which ended with a recommended change in ART. Uncertainty over the time for resolution of gynaecomastia remains and is influenced by aetiology; idiopathic gynecomastia in children takes 0.8 – 2.6 years to resolve [12]. In adults gynaecomastia can be a transient phenomenon possibly reflecting a form of immune reconstitution [4] or resolve within a mean of ~5 months after withdrawal of EFV [2]. In a cohort of HIV-infected adult males on a variety of ART combinations (55% EFV) 20/21 of those followed for over a year had spontaneous resolution

within 17 months (mean, 8.8 months) without modification of ART [13]. Substantial resolution is unlikely if gynaecomastia persists for more than a year as fibrotic tissue is usually present [14]. Whilst rare it must be remembered that malignancy, especially lymphoma, can also present as breast enlargement [15].

## **Conclusions**

The overall prevalence of severe gynaecomastia in children and young people living with HIV was 0.5%; most had been exposed to ART drugs known to be associated with the condition. Timely recognition of true drug-induced gynaecomastia offers the possibility of non-invasive intervention as reversibility is more likely if gynaecomastia has developed recently. The higher prevalence in males and a single severe case in a female may reflect the difficulty in diagnosing severe gynaecomastia in peri-pubertal females. Considering the devastating potential impact of this condition on adherence in perinatally HIV-infected adolescents, prompt identification is important. Uncertainty remains over optimal management and it is critical to involve the patient in the decision making process. In our study, severe cases were more likely to have a low or normal BMI; in those with a higher BMI or just starting treatment, adult data suggest a watch and wait approach for a period of up to 9 months may be appropriate. However, where alternative treatments are available, an early switch to ART combinations with a more favourable metabolic profile is recommended.

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**Author contributions:**

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