Published in final edited form as:
Pediatr Infect Dis J. 2017 March ; 36(3): 307–310. doi:10.1097/INF.0000000000001424.

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

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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.

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).

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Author contributions:
All authors were responsible for the study concept and design. Julia Kenny, Katja Doerholt and Di Gibb collected the data. Julia Kenny carried out the statistical analyses. All authors drafted the manuscript, and participated in discussions about the design of the study, interpretation of the findings, and critically reviewed the manuscript.

Conflicts of interest: No conflicts of interest declared.

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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), ddI (6) and tenofovir (2). All 10 had previous or current exposure to d4T, ddI and/or EFV (7 d4T for a median of 42 [21, 74] months, 7 ddI 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.

Acknowledgements

CHIPS Steering Committee:, K Butler, K Doerholt, S Donaghy, C Foster, DM Gibb, A Judd, J Kenny, N Klein, EGH Lyall, , E Menson, K Prime, A Riordan, F Shackley, M Sharland, D Shingadia, PA Tookey, G Tudor-Williams, S Welch

MRC Clinical Trials Unit: IJ Collins, C Cook, K Doerholt, DM Gibb, A Judd, L Harper, A Tostevin, D Dobson, K Bellenger, D Johnson.

National Study of HIV in Pregnancy & Childhood, UCL Institute of Child Health: PA Tookey, H Peters

We thank the staff, families & children from the following hospitals who participate in CHIPS (in alphabetical order):

Republic of Ireland: **Our Lady's Children's Hospital Crumlin**, Dublin: K Butler, A Walsh. **UK**: **Birmingham Heartlands Hospital**, Birmingham: S Scott, Y Vaughan, S Welch; **Blackpool Victoria Hospital**, Blackpool: N Laycock; **Bristol Royal Hospital for Children**, Bristol: J Bernatoniene, A Finn, L Hutchison; **Calderdale Royal Hospital**, Halifax: G Sharpe; **Central Middlesex Hospital**, London: A Williams; **Chelsea and Westminster Hospital**, London: EGH Lyall, P Seery; **Coventry & Warwickshire University Hospital**, Coventry: P Lewis, K Miles; **Derbyshire Children's Hospital**, Derby: B Subramaniam; **Derriford Hospital**, Plymouth: L Hutchinson, P Ward; **Ealing Hospital**, Middlesex: K Sloper; **Eastbourne District General Hospital**, Eastbourne: G Gopal; **Glasgow Royal Hospital for Sick Children**, Glasgow: C Doherty, R Hague, V Price; **Great Ormond St Hospital for Children**, London: H Bundy, M Clapson, J Flynn, DM Gibb, N Klein, V Novelli, D Shingadia; **Halliwell Children's Centre,** Bolton: P Ainsley-Walker; **Harrogate District Hospital,** Harrogate: P Tovey; **Homerton University Hospital**, London: D Gurtin; **Huddersfield Royal Infirmary**, Huddersfield: JP Garside; **James Cook Hospital**, Middlesbrough: A Fall; **John Radcliffe Hospital**, Oxford: D Porter, S Segal; **King's College Hospital**, London: C Ball, S Hawkins; **Leeds General Infirmary**, Leeds: P Chetcuti, M Dowie; **Leicester Royal Infirmary**, Leicester: S Bandi, A McCabe; **Luton and Dunstable Hospital**, Luton: M Eisenhut; **Mayday University Hospital**, Croydon: J Handforth; **Milton Keynes General Hospital**, Milton Keynes: PK Roy; **Newcastle General Hospital**, Newcastle: T Flood, A Pickering; **Newham General Hospital**, London: S Liebeschuetz; **Norfolk & Norwich Hospital**, Norwich: C Kavanagh; **North Manchester General Hospital**, Manchester: C Murphy, K Rowson, T Tan; **North Middlesex Hospital**, London: J Daniels, Y Lees; **Northampton General Hospital**, Northampton: E Kerr, F Thompson; **Northwick Park Hospital** Middlesex; M Le Provost, A Williams; **Nottingham City Hospital**, Nottingham: L Cliffe, A Smyth, S Stafford; **Queen Alexandra Hospital**, Portsmouth: A Freeman; **Raigmore Hospital**, Inverness: T Reddy; **Royal Alexandra Hospital**, Brighton: K Fidler; **Royal Belfast Hospital for Sick Children,** Belfast: S Christie; **Royal Berkshire Hospital**, Reading: A Gordon; **Royal Children's Hospital**, Aberdeen: D Rogahn; **Royal Cornwall Hospital**, Truro: S Harris, L Hutchinson; **Royal Devon and Exeter Hospital**, Exeter: A Collinson, L Hutchinson; **Royal Edinburgh Hospital for Sick Children**, Edinburgh: L Jones, B Offerman; **Royal Free Hospital**, London: V Van Someren; **Royal Liverpool Children's Hospital**, Liverpool: C Benson, A Riordan; **Royal London Hospital**, London: A Riddell; **Royal Preston Hospital**, Preston: R O'Connor; **Salisbury District General Hospital,** Salisbury: N Brown; **Sheffield Children's Hospital**,

Sheffield: L Ibberson, F Shackley; **Southampton General Hospital,** Southampton: SN Faust, J Hancock; **St George's Hospital**, London: K Doerholt, S Donaghy, K Prime, M Sharland, S Storey; **St Luke's Hospital**, Bradford: S Gorman; **St Mary's Hospital**, London: EGH Lyall, C Monrose, P Seery, G Tudor-Williams, S Walters; **St Thomas' Hospital (Evelina Children's Hospital)**, London: R Cross, E Menson; **Torbay Hospital**, Torquay: J Broomhall, L Hutchinson; **University Hospital Lewisham**, London: D Scott, J Stroobant; **University Hospital of North Staffordshire**, Stoke On Trent: A Bridgwood, P McMaster; **University Hospital of Wales**, Cardiff: J Evans, T Gardiner; **Wexham Park**, Slough: R Jones; **Whipps Cross Hospital**, London: K Gardiner;

source of funding: The National Study of HIV in Pregnancy and Childhood is funded by Public Health England (formerly the Health Protection Agency) and has received additional support from the Welton Foundation, the National Screening Committee and AbbVie. The Collaborative HIV Paediatric Study is funded by the NHS (London Specialised Commissioning Group) and has received additional support from the PENTA Foundation as well as Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen and Roche. The views expressed in the publication are those of the authors and not necessarily those of Public Health England or the London NHS Specialised Commissioning Group, or any of the additional funders.

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Pediatr Infect Dis J. Author manuscript; available in PMC 2018 May 01.

Table 1

Details of the Patients With Severe Gynecomastia

Age at Onset (yr)	Sex (M/F)	Ethinicity	ART at Onset	Duration on Current ART Regimen (mo)	Previous ART	Cumulative ART Exposure (mo)	Cumulative Exposure to Specific Drug at Onset (mo)			BMI	Tanner Stage at Onset	Other Signs of Lipodystrophy	Management	Outcome
							d4T	ddI	EFV					
8	M	Black African	d4T 3TC NFV	88	ddI	88	84	12	0	healthy	NK	Moderate abdominal lipohypertrophy, mild lipoatrophy	ART stopped	Resolved within 2 yr
9	M	Black African	d4T 3TC NFV	74	ddI	96	74	22	0	healthy	3	Mild abdominal lipohypertrophy	d4T switched to ABC, observed for 15 mo then ART stopped	Resolved within 2 yr
12	M	White	d4T 3TC LPV/r	31	Nil	31	31	0	0	healthy	NK	Severe neck and abdominal lipohypertrophy, mild lipoatrophy	d4T switched to ABC, observed 3 mo then ART stopped	Resolved within 2 yr
13	M	Black African	ddI d4T LPV/r	42	Nil	42	42	42	0	Under-weight	3/4	Moderate lipoatrophy	Switched to ZDV 3TC NVP, with no improvement, ZDV switched to ABC, no change	Breast reduction surgery 15 yr of age
13	M	Black African	ABC TDF NVP	14	ZDV, 3TC, ddI, d4T, NFV	153	21	21	0	healthy	1	Mild abdominal lipohypertrophy	Observed	Breast reduction surgery 15 yr of age
14	M	Black African	ddI 3TC LPV/r	21	Nil	21	0	21	0	Under-weight	NK		Observed 4 mo testosterone gel, ART changed to LPV/R monotherapy	Breast reduction surgery 16 yr of age
14	M	Black African	TDF FTC EFV	9	ZDV, ddI, 3TC, d4T, NFV	63	57	0	10	Under-weight	3/4		Observed plus endocrine review, offered treatment switch but refused	Ongoing, considering surgery
14	F	Mixed race	ABC 3TC EFV	24	Nil	24	0	0	28	Healthy	4		Observed 4 mo then EFV switched to NVP	Breast reduction surgery 16 yr of age
15	M	Black African	ddI d4T EFV	24	ABC, 3TC, NFV	58	15	15	30	Under-weight	NK		Observed 6 mo with topical testosterone cream then EFV switched to TDF	Breast reduction surgery 16 yr of age
17	M	White	ABC 3TC EFV	36	NFV	72	0	0	48	Over-weight	5	Moderate abdominal lipohypertrophy	Observed	Still present after 3 yr, moved to adult HIV clinic, final outcome unknown

3TC indicates lamivudine; ABC, abacavir; ART, antiretroviral therapy; BMI, body mass index; d4T, stavudine; ddI, didanosine; EFV, efavirenz; LPV/r, ritonavir boosted lopinavir; NFV, melfinavir; NK, not known; NVP, nevirapine; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.