Breast Abnormalities in Adolescents receiving Antiretroviral Therapy

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Introduction

• Gynaecomastia related to ART in adult males is well documented

• Few studies have described this phenomenon in adolescents

• In a UK study, 3% (56/1873) of a paediatric and adolescent HIV clinic cohort developed gynaecomastia/breast hypertrophy\(^1\)

• In South Africa, one case of a prepubescent girl who developed EFV-related gynaecomastia was documented\(^2\)

2. van Ramshorst MS et al, BMC Pediatr, 2013
The Past...

HIV-infected adolescents on anti-retroviral therapy: a retrospective descriptive cohort study of breast abnormalities documented during routine care

Jackie Dunlop, Cynthia Firnhaber, Wiedaad Slemming, Kathryn Schnippel, Caroline Makura, Sarah Rayne, Leon Levin
Hypothesis

Hypothesis: Are particular antiretrovirals related to the development of breast conditions in adolescents with HIV?

Dzwonek A et al, Pediatr Infect Dis J. 2006
### Methods

<table>
<thead>
<tr>
<th>Study Description</th>
<th>• Retrospective review of routinely collected medical records</th>
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<tbody>
<tr>
<td>Study population</td>
<td>• Patients aged 10-19 on ART</td>
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<td>• Presented at clinics from 1 January to 31 December 2014</td>
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<td>Study sites</td>
<td>• 3 ARV sites in Johannesburg</td>
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<td>Focus of review</td>
<td>• Reviewed records for reference of “breast” and then described information surrounding event</td>
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Results - Gender

• There were significantly more “abnormally” defined breast events in males (p=0.043)

• In this cohort:
  – 47% of normal breast events occurred in males compared to
  – 66% of “abnormal” breast events occurred in males
Results - Age

p<0.0005

minimum and maximum age unavailable

Results – Abnormalities

All included patients

Normal breast development (594)

Abnormal breast...

- No description: 1
- Breast lump: 1
- Gynaecomastia/Lipomastia: 3
- Lipomastia: 4
- Gynaecomastia: 12
- Breast buds: 2
- Enlargement: 18

41 abnormal breast events
Results – ART exposure

• All 37 patients with abnormal breast enlargement had received EFV
  – Median time of 5.5 years (IQR 3.8-8.5)

• 60% had received D4T (n=22/37)
  – Median time of 4.9 years (IQR 1.8-7.2)
Results: Adherence

Objectively

- 70% of patients had:
  - CD4 counts higher than 500 and
  - Virologically suppressed as defined by a viral load of 50 copies/ml or fewer

Subjectively

Good adherence defined as patient or patient caregiver self-report that
gerreater than 90% of doses were administered
63.4% of patients with abnormal breast conditions reported good adherence
Comparison with other gynaecomastia studies

**IRIS**
- **HYPOTHESIS**: Gynaecomastia is caused by an IRIS phenomenon
- IRIS most common in first 6 months of starting/changing regimen
- Median exposure time to ART before breast abnormalities 4.9 years
- **IRIS is an unlikely aetiology in this cohort**

  Qazi NA et al, AIDS, 2002

**Hypogonadism**
- **HYPOTHESIS**: Gynaecomastia caused by HIV-related hypogonadism
- One patient who developed breast abnormalities was receiving hormone injections
- **Not well explored in this cohort**

  Biglia A et al, Clin Infect Dis, 2004

**Lipodystrophy**
- **HYPOTHESIS**: Breast abnormalities are part of fat accumulation associated with some ARVs
- Sonography cannot sufficiently distinguish fatty/glandular predominance
- 46% (19/41) of breast abnormalities experienced in patients with co-morbid lipodystrophy

Comparison with other gynaecomastia studies

Pubertal gynaecomastia

• **HYPOTHESIS:** Gynaecomastia is caused by normal pubertal hormonal changes
• 4-69% of adolescent males report an increase in breast size
• Peak age between 13 and 14 years old
• **Breast abnormalities were reported later in this cohort (15.5 years)**
• **Supported by UK CHIPS cohort (15 years)**
  
  Lemaire V et al, *Semin Plast Surg*, 2013

Oestrogen receptor activation by EFV

• **HYPOTHESIS:** EFV use causes breast abnormalities
• Current use of EFV was associated with the onset of breast abnormalities (p<0.0005)
• All patients had received EFV as part of their current or a previous regimen
• **Substitution of EFV led to resolution of the condition in 3/17 cases**
• **No other intervention led to resolution**
  
  van Ranghorst MS et al, *BMC Pediatr*, 2013
Interventions

• Drug substitution – Remove EFV and D4T from patients’ regimens
• Lifestyle changes
• Tamoxifen (selective oestrogen receptor modulator)
• Referral to specialist clinics
Study limitations

• No control group

• Reliance on clinician reporting of breast abnormalities during routine consultation

• Substantial interaction between clinicians at all three sites may have led to similar management of abnormal breast conditions
Study Conclusions

- 6% of patients aged 10 – 19 years on ART had experienced breast abnormalities
- Strong significance associated with breast abnormalities in adolescents on ART:
  - EFV use
  - Older age
- Only half received an intervention with a drug substitution being the most common
- Phenomenon likely ARV-related (EFV), interacting with pubertal hormonal changes
The Present...

Adolescent Breast Clinic at Helen Joseph Hospital (2014 – 2018)

• Referrals and self-referrals from surrounding clinics
• Specialist breast surgeon, plastic surgeon, HIV doctor, Psychologist/Social Worker
Algorithm for managing patients

1) Substitute all patients off EFV and/or D4T
   • No longer suggest NVP as an alternative
   • Recommend Aluvia (once daily) or Atazanavir be used
   • Rilpivirine is an excellent option for those who can buy (SA: Use from 18 years, US from 12 years)
   • Rule out other medicines that could be contributing (anabolic steroids, corticosteroids, spirinolactone)
   • Allow 6 months on the new regimen
Algorithm for managing patients

2) Give Tamoxifen

- 10mg given once daily for 6 months
  *will need to break the tablet
- Used for anti-oestrogen effects
- Can be given to boys and girls complaining of breast enlargement
- May reduce breast size and breast pain
- Less likely to resolve if breast enlargement >6 months due to fibrous changes
Algorithm for managing patients

3) Refer to Plastic Surgery Breast Clinic
Thursdays at HJH Breast Clinic
Breast sonography will be done
Stable with suppressed VL and good CD4
Assent and Consent - counselling
Algorithm for managing patients

4) When to further investigate

• Symptoms (e.g. bleeding or nipple discharge),
• Presence of systemic disease (especially liver, kidney, adrenal, thyroid, pituitary glands, testes, and prostate),
• History of recent weight change,
• Presence of risk factors for breast cancer

Lemaine V et al, Semin Plast Surg, 2013
The Future...

- Dolutegravir – What about the adolescent girls??
- EFV may be here to stay
- Must be aware of breast abnormalities in adolescents
  - Ask about them routinely
  - Examine patients for them
  - Refer appropriately after ART switch (may need expert support)
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  – Drs Leon Levin, Marnie Vujovic, Sanlie Untiedt, Melanie Collins and Julia Turner
References


