



# 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<sup>1</sup>
- In South Africa, one case of a prepubescent girl who developed EFV-related gynaecomastia was documented<sup>2</sup>

1. Kenny J et al, *Pediatr Infect Dis J*, 2016

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

## Study Description

- Retrospective review of routinely collected medical records

## Study population

- Patients aged 10-19 on ART
- Presented at clinics from 1 January to 31 December 2014

## Study sites

- 3 ARV sites in Johannesburg

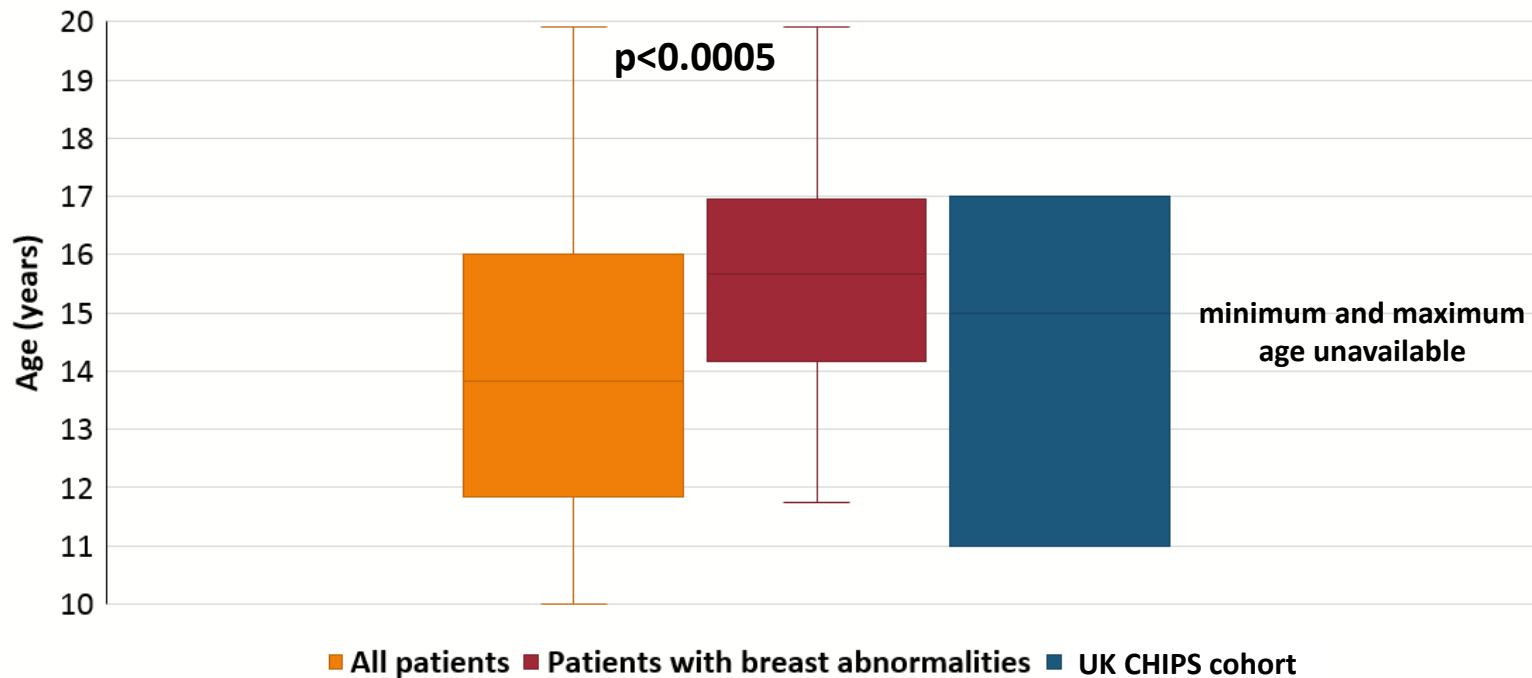
## Focus of review

- Reviewed records for reference of “breast” and then described information surrounding event

# Results - Gender

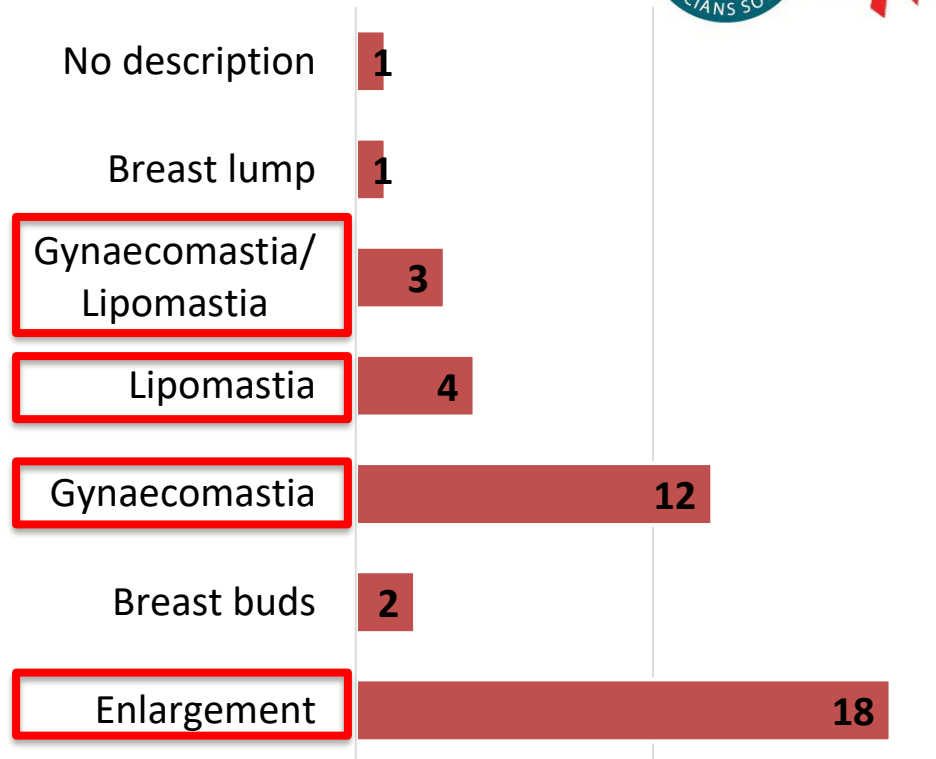
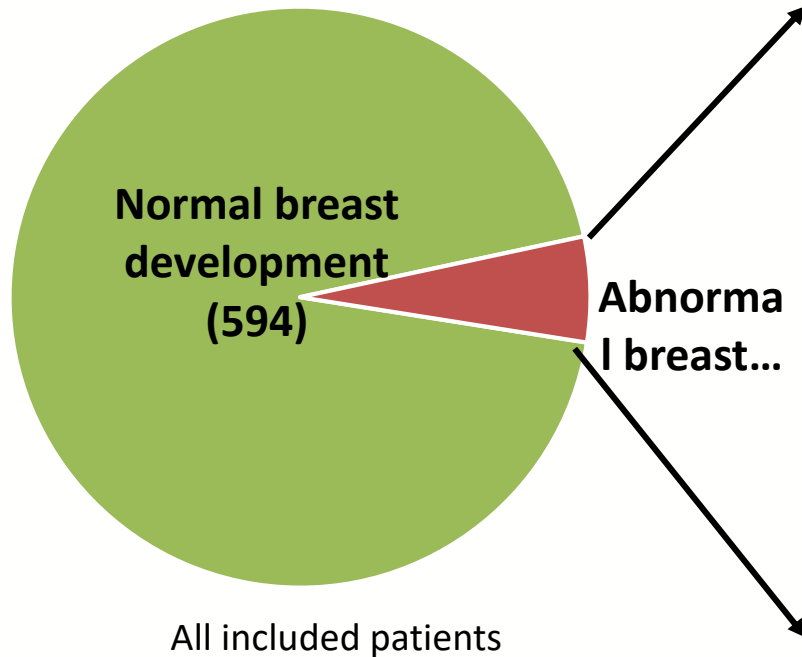
- There were significantly more “abnormally” defined breast events in males ( $p=0.043$ )
- In this cohort:
  - 47% of normal breast events occurred in males  
compared to
  - 66% of “abnormal” breast events occurred in  
males

# Results - Age





# Results – Abnormalities



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 **greater 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

Rossouw T et al, South Afr J HIV Med, 2013

# 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)**

Lemaine V et al, *Semin Plast Surg*,  
2013

Kenny J et al, *Pediatr Infect Dis J*, 2016

## 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**

Mercié P et al, *AIDS*, 2001

van Ramshorst 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

# 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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- Right to Care Paediatric Team
  - Drs Leon Levin, Marnie Vujovic, Sanlie Untiedt, Melanie Collins and Julia Turner



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