British HIV Association
BHIVA

Dr John Quin

Royal Sussex County Hospital, Brighton

COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Dr John Quin	None
Date	**November 2013**

CLINICAL CASES AND QUESTIONS FROM A JOINT HIV ENDOCRINE CLINIC

Dr Debbie Williams, Consultant GUM/HIV
Dr John Quin, Consultant Endocrinologist

brighton and sussex medical school

Brighton and Sussex University Hospitals NHS Trust

Background

Endocrine problems in HIV	
Pre HAART era	Advanced disease
	Opportunistic infections
	Tumours
Early HAART era	Metabolic complications of ARV's
	Lipodystrophy, Insulin resistance
Late HAART era	Age related Drug interactions IRIS

Slide 3

1 deborah williams, 08/11/2013

Case 1

45 yr MSM

HIV+ 10 yrs

VL<40 CD4 450

On Truvada, darunavir/ritonavir

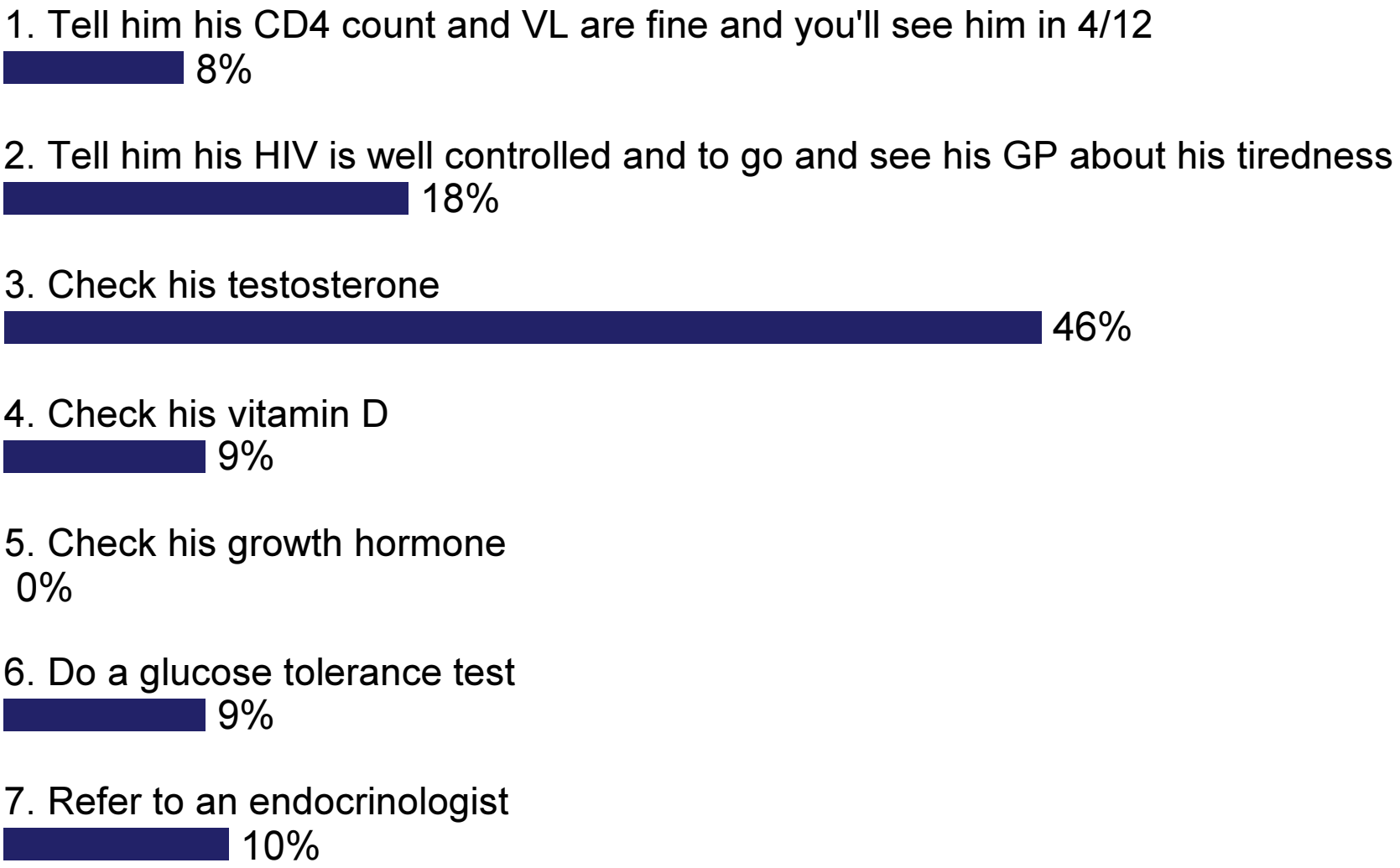
Lipodystrophy

c/o fatigue, ‘tired all the time’ (TATT), poor libido, erectile dysfunction, low mood

Question 1: What do you do with a “tired all the time”?

1. Tell him his CD4 count and VL are fine and you’ll see you in 4/12
2. Tell him his HIV is well controlled and to go and see his GP about his tiredness
3. Check his testosterone
4. Check his vitamin D
5. Check his growth hormone
6. Do a glucose tolerance test
7. Refer to an endocrinologist

Question 1: What do you do with a “tired all the time”?



TATT screen

Male	Female
Testosterone - 08.00 Cortisol - 08.00 Thyroid function Fasting glucose	Cortisol - 08.00 Thyroid function Fasting glucose Female hormones if amenorrhea

Vitamin D, Vitamin B12 & folate, Fe studies

Case: Results

Testosterone - random

Total testosterone: 9.5 (9.47-28.3 nmol/l)

SHBG: 88 (21-77nmol/l)

Thyroid function

T4: 10 (12-22 pmol/l)

TSH: 2.4 (0.3-4.2)

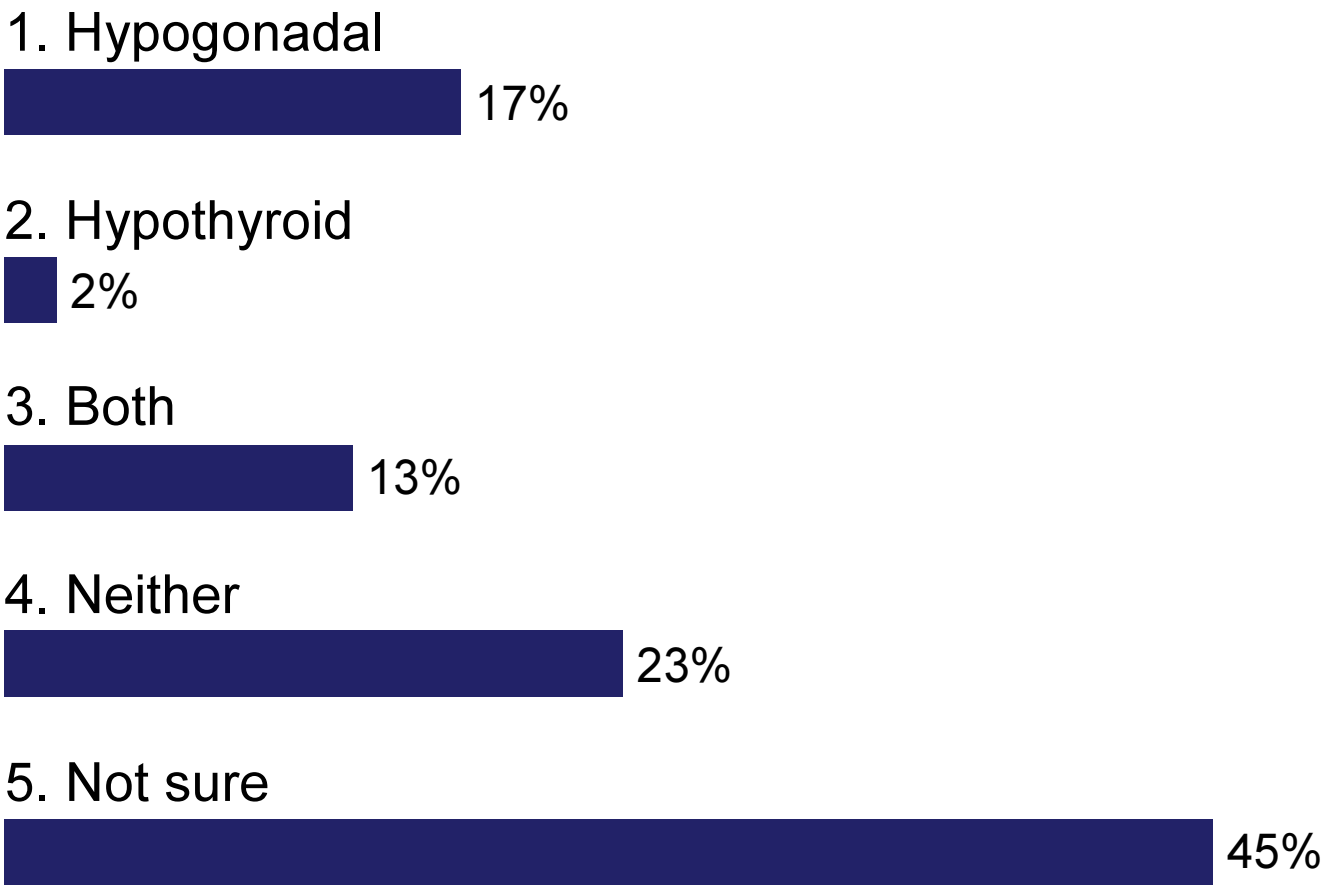
Cortisol: 470 (171-536)

Glucose: 5.0

Question 2: Is he hypogonadal and /or hypothyroid?

1. Hypogonadal
2. Hypothyroid
3. Both
4. Neither
5. Not sure

Question 2: Is he hypogonadal and /or hypothyroid?



Case: Results

Testosterone

Total testosterone: 9.5 (9.47-28.3 nmol/l)

SHBG: 88 (21-77nmol/l)

Free testosterone: 163 (185-437pmol/l)

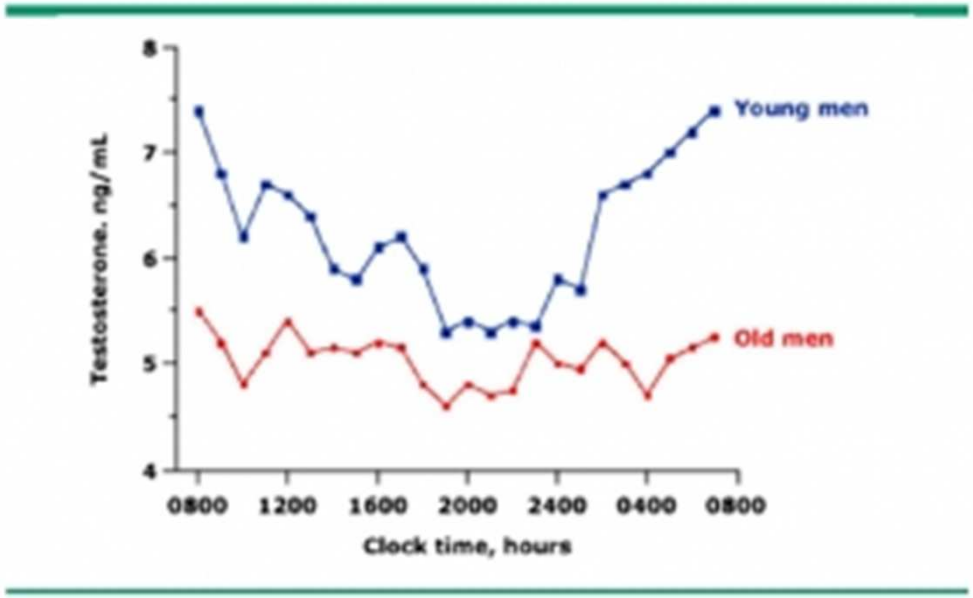
Thyroid function

T4: 10 (12-22 pmol/l)

TSH: 2.4 (0.3-4.2)

Cortisol: 470 (171-536)

Glucose: 5.0



What next?

Repeat 08.00

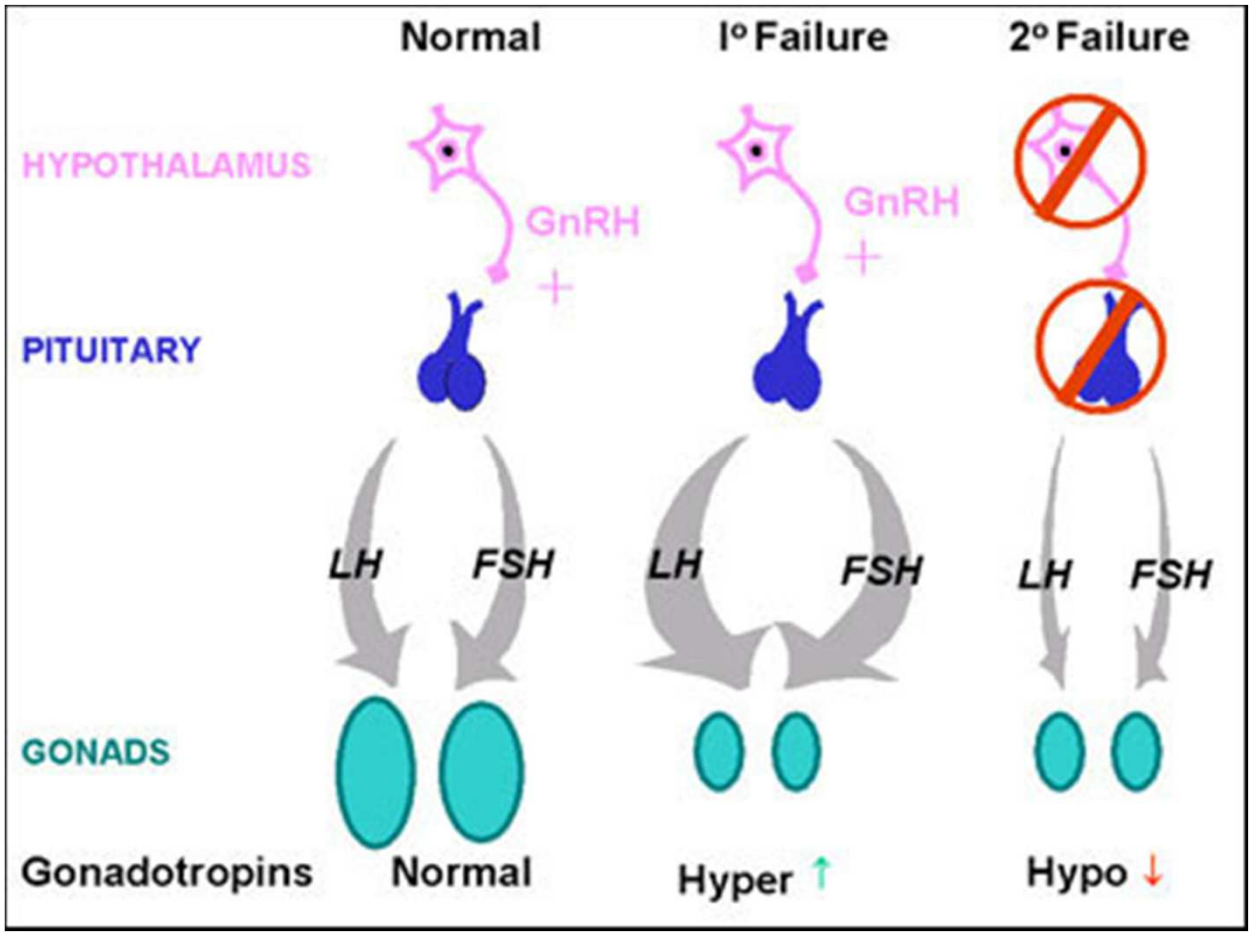
Testosterone

Plus:

LH

FSH

Prolactin



Case: Results

Total testosterone:	10.0	(9.47-28.3 nmol/l)
SHBG:	88	(21-77 nmol/l)
Free testosterone:	165	(185-437 pmol/l)
LH :	1.9	(1.7 – 8.6 iu/l)
FSH:	4.9	(1.5-12.0 iu/l)
Prolactin:	110	(86-234 miu/ml)

Management

- Who?
  - Threshold, age
- What with?
  - Injectables vs gel/patches
- Monitoring?
  - What
  - Whose job is it
- What should improve?
  - Duration
- Risks?

Slide 14

7 ? new slide of which therapeutic options? include nil…..

slide on monitoring and other investigations - PSA, DEXA, therapeutic goal - clinical? hormonal? - is it forever?

whose job is it?
does everyone need to see an endocrinologist?
whats the role of the GP?
Martin Mortgage, 08/11/2013

What about his thyroid function?

T4: 10 (12-22 pmol/l)

TSH: 2.4 (0.3-4.2)

Sick euthyroidism?

- Repeat TFT's plus
  - thyroid autoantibodies
  - T3
  - Cortisol

- No indication for T4
- Monitor

Case 2

- 52 yr MSM
- HIV+ 15 yrs
- Long ARV history
- VL<40 on Truvada/darunavir/ritonavir
- Impaired glucose tolerance
- Hyperlipidaemia
- c/o Fatigue
- TATT screen : normal

Has seen adverts for growth hormone on the internet and wants to take it

Question 3: How many patients have you tested for growth hormone deficiency in the last year?

1. 1-5
2. 6-10
3. >10
4. None

Question 3: How many patients have you tested for growth hormone deficiency in the last year?

Symptoms & signs of GH deficiency

- Fatigue
- Changes in memory and concentration
- Depression, Anxiety
- Insomnia
- Fibromyalgia syndrome
- Central adiposity, decreased muscle mass & bone density
- Decreased insulin sensitivity
- Accelerated atherogenesis, increased LDL
- Prothrombotic state
- Decreased sweating and thermoregulation

Slide 20

8 ? Question sfirst - how many have you screened for HGH deficiency?

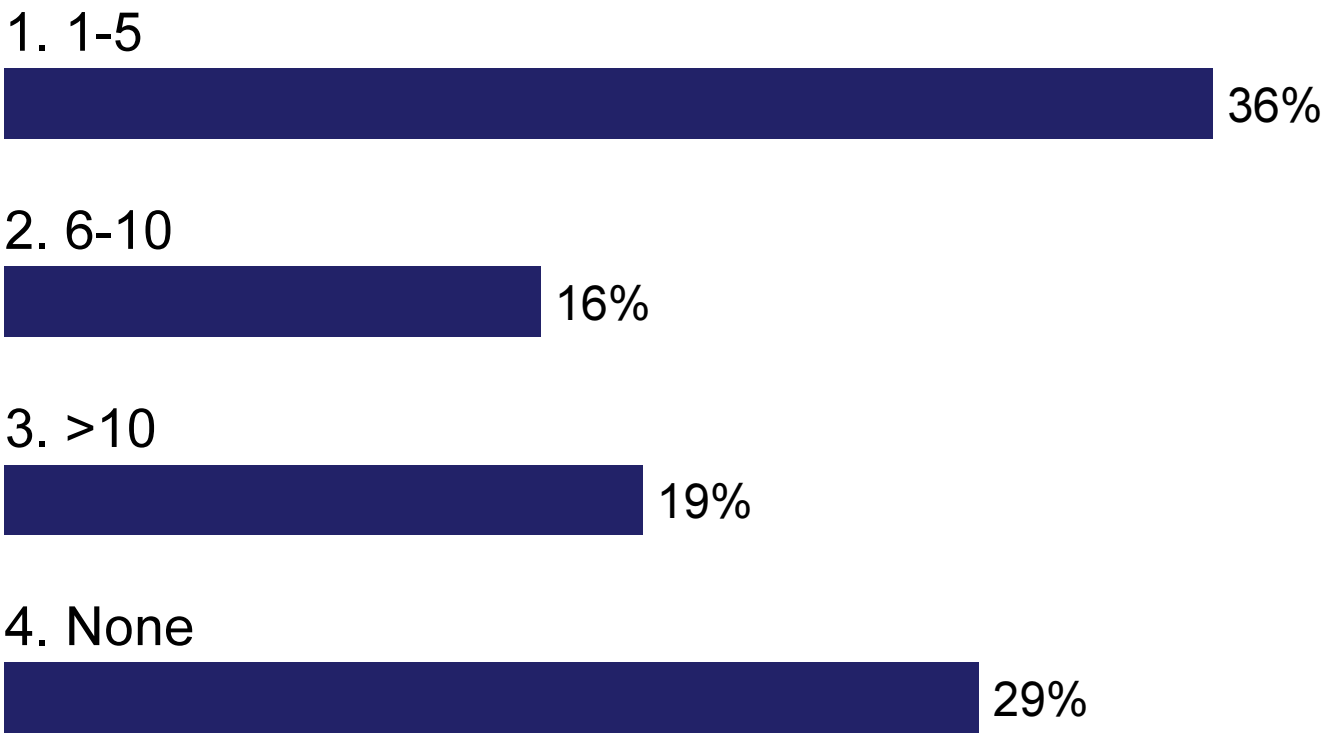
Show this slide

Then repeat the question!
Martin Mortgage, 08/11/2013

Question 4: How many patients do you think you will test for growth hormone deficiency in the next year?

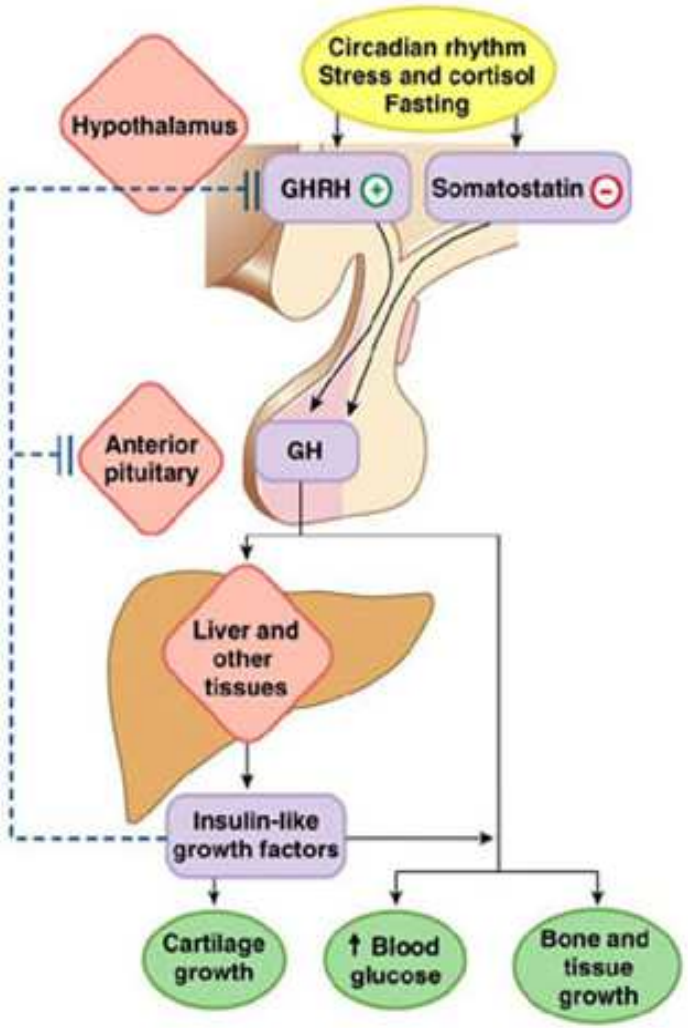
1. 1-5
2. 6-10
3. >10
4. None

Question 4: How many patients do you think you will test for growth hormone deficiency in the next year?



Growth hormone

- GH
  - Released in pulses
  - Breaks down fat
  - Gluconeogenesis
  - Stimulates insulin like GF from liver
  - Muscle building
  - Bone growth



Growth hormone

- Who should we test?
  - Only those with documented evidence of pituitary dysfunction
  - Only those already optimally treated with other hormones

- How to test ?
  - IGF1
  - Arginine stimulation
  - Insulin stress test

Case: Results

Arginine stimulation test	
Time (minutes)	Growth hormone (ug/l)
0	<0.1
30	2.3
45	2.9
60	2.9
75	1.7
90	1.3
105	1.2
120	0.8
Normal: increase to >9 ug/l	
IGF-1	17.6 (7.0 - 25)

Endocrine screen	
FSH	5.0 (1.5-12)
LH	6.0 (1.7-8.6)
prolactin	300 (86-324)
TSH	2.0 (0.3-4.2)
T4	10 (12-22)
Cortisol	420 (170-570)
Glucose	9

Management

- Who to consider treating
- GH therapy practical issues?
  - Monitoring
  - Risks

Case 3

- 35 yr HIV+ woman
- On Truvada/Atazanavir/Ritonavir
- VL<40 CD4 600
- Fibromyalgia/seronegative spondyloarthropathy
- c/o 4/52 history fatigue, proximal myopathy, polydypsia and polyuria, weight gain

Given Kenalog® intra articularly 6/52 ago

Examination & investigations

Cushingoid appearance

Central obesity

Proximal myopathy

BP : 130/90

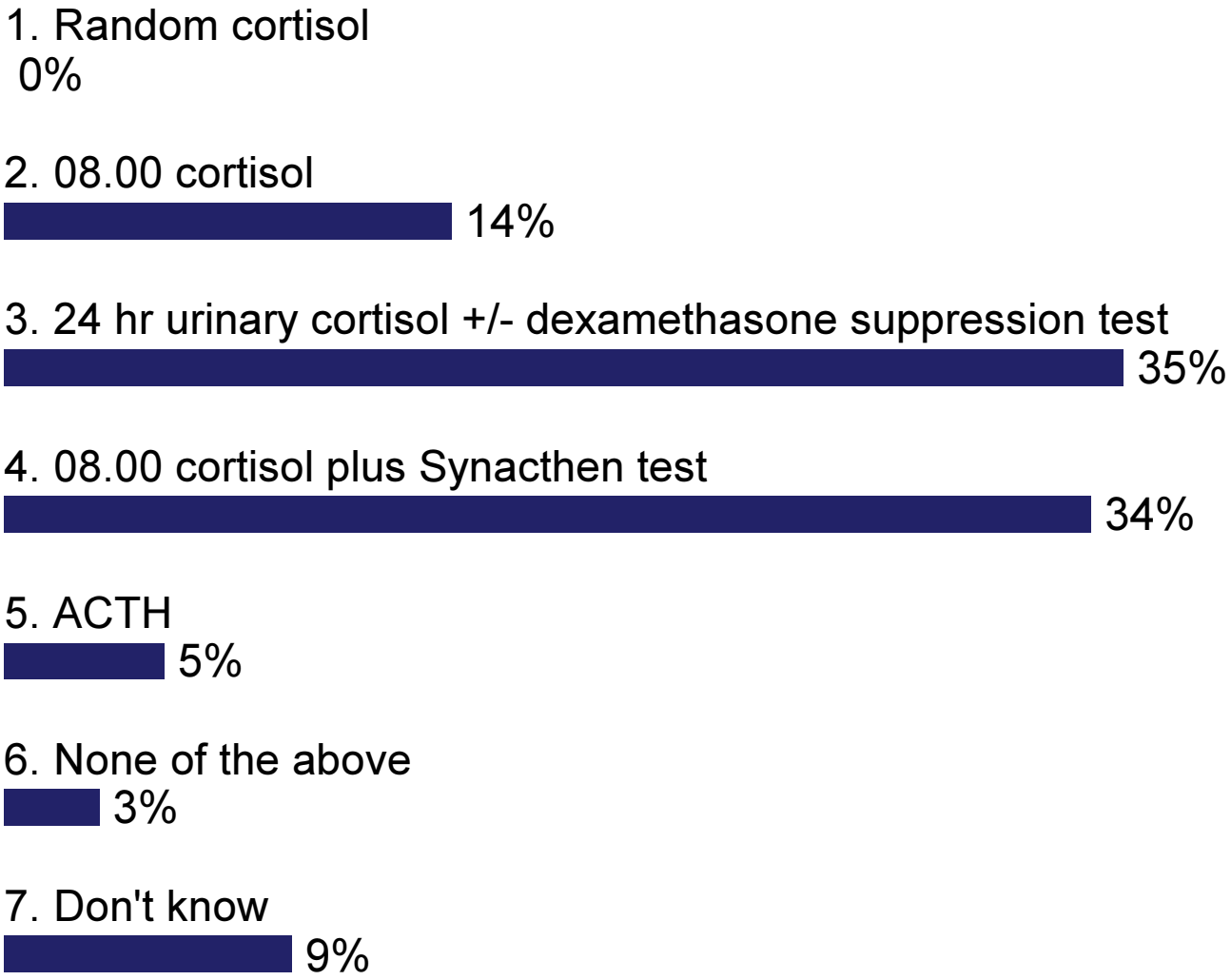
results	
glucose	20 mmol/l
FBC	normal
K	low
LFT	normal
TFT	normal

9 Question of what test - clinical diagnosis is iatrogenic Cushings - what test to prove?
what to test to decide whether intervention necessary?
Martin Mortgage, 08/11/2013

Question 5: What test would you do to confirm the diagnosis?

1. Random cortisol
2. 08.00 cortisol
3. 24 hr urinary cortisol +/- dexamethasone suppression test
4. 08.00 cortisol plus Synacthen test
5. ACTH
6. None of the above
7. Don’t know

Question 5: What test would you do to confirm the diagnosis?



Case: Results

Random cortisol: 14 (171- 536 nmol/l)

Synacthen test	
Time (minutes)	Cortisol nmol/l
0	7
30	120

Normal:

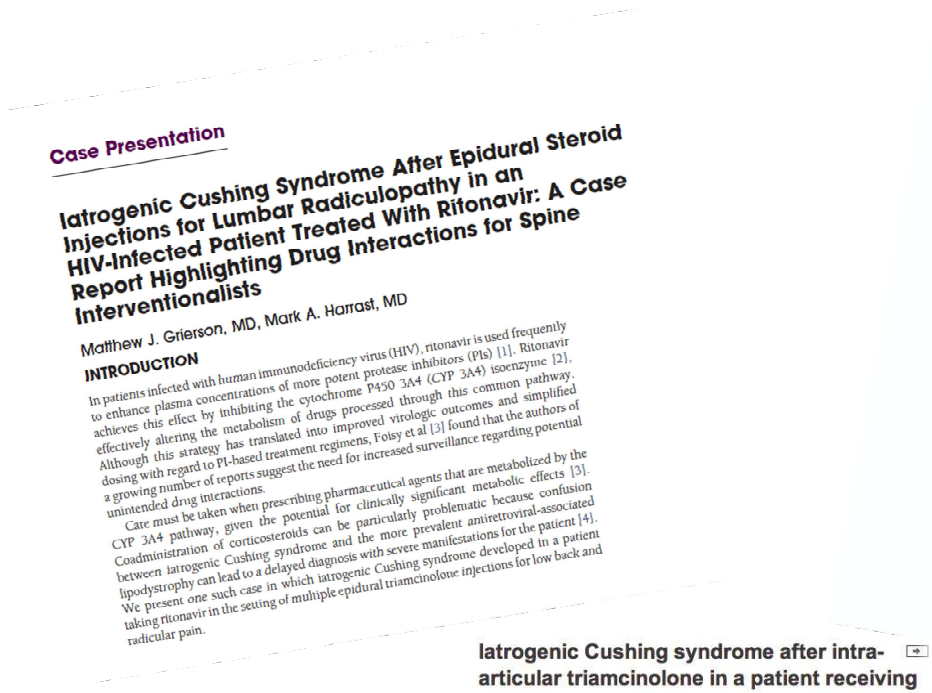
- Rise of >200nmol between 0-30 min.
- >550nmol/l at 30 min

Slide 31

10 drop the HbA1c; give nomral ranges

Martin Mortgage, 08/11/2013

Iatrogenic cushings with secondary adreno-cortical suppression



Case Presentation

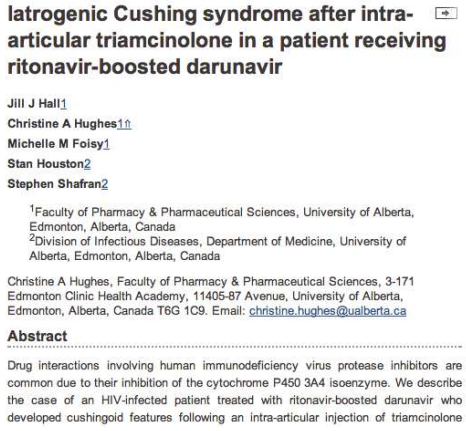
Iatrogenic Cushing Syndrome After Epidural Steroid Injections for Lumbar Radiculopathy in an HIV-Infected Patient Treated With Ritonavir: A Case Report Highlighting Drug Interactions for Spine Interventionalists

Matthew J. Grierson, MD, Mark A. Harrast, MD

INTRODUCTION

In patients infected with human immunodeficiency virus (HIV), ritonavir is used frequently to enhance plasma concentrations of more potent protease inhibitors (PIs) [1]. Ritonavir achieves this effect by inhibiting the cytochrome P450 3A4 (CYP 3A4) isoenzyme [2], effectively altering the metabolism of drugs processed through this common pathway. Although this strategy has translated into improved virologic outcomes and simplified dosing with regard to PI-based treatment regimens, Foisy et al [3] found that the authors of a growing number of reports suggest the need for increased surveillance regarding potential unintended drug interactions.

Care must be taken when prescribing pharmaceutical agents that are metabolized by the CYP 3A4 pathway, given the potential for clinically significant metabolic effects [3]. Coadministration of corticosteroids can be particularly problematic because confusion between Iatrogenic Cushing syndrome and the more prevalent antiretroviral-associated lipodystrophy can lead to a delayed diagnosis with severe manifestations for the patient [4]. We present one such case in which Iatrogenic Cushing syndrome developed in a patient taking ritonavir in the setting of multiple epidural triamcinolone injections for low back and radicular pain.



Iatrogenic Cushing syndrome after intra-articular triamcinolone in a patient receiving ritonavir-boosted darunavir

Jill J Hall[1]

Christine A Hughes[1]*

Michelle M Foisy[1]

Stan Houston[2]

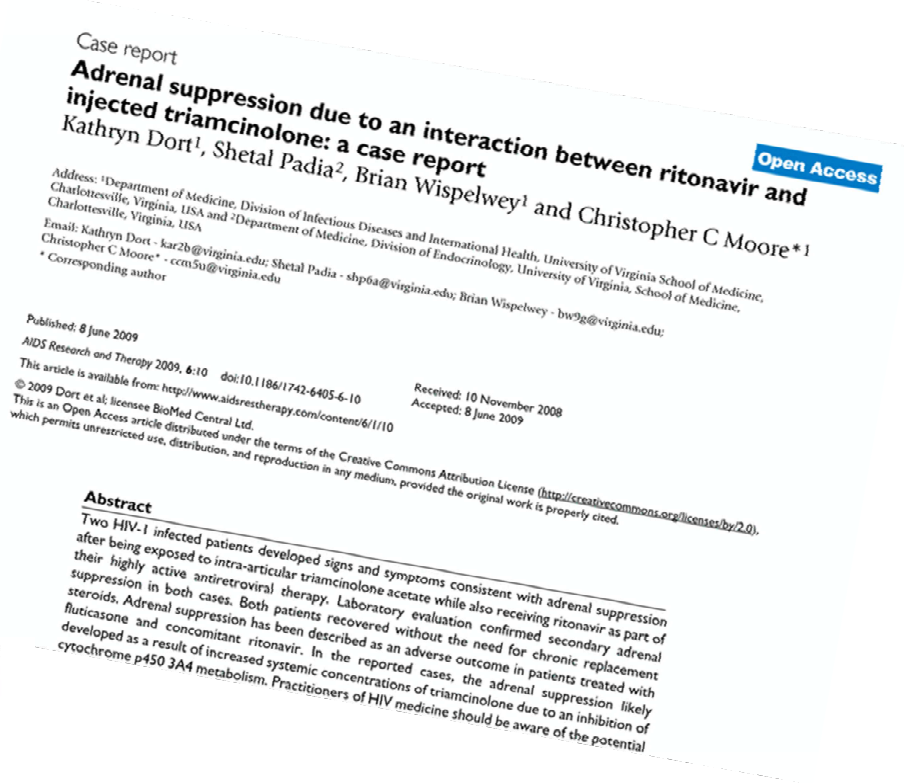
Stephen Shafran[2]

[1]Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada
[2]Division of Infectious Diseases, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada

Christine A Hughes, Faculty of Pharmacy & Pharmaceutical Sciences, 3-171 Edmonton Clinic Health Academy, 11405-87 Avenue, University of Alberta, Edmonton, Alberta, Canada T6G 1C9. Email: christine.hughes@ualberta.ca

Abstract

Drug interactions involving human immunodeficiency virus protease inhibitors are common due to their inhibition of the cytochrome P450 3A4 isoenzyme. We describe the case of an HIV-infected patient treated with ritonavir-boosted darunavir who developed cushingoid features following an intra-articular injection of triamcinolone



Case report

Adrenal suppression due to an interaction between ritonavir and injected triamcinolone: a case report

Open Access

Kathryn Dort[1], Shetal Padia[2], Brian Wispelwey[1] and Christopher C Moore*[1]

Address: [1]Department of Medicine, Division of Infectious Diseases and International Health, University of Virginia School of Medicine, Charlottesville, Virginia, USA and [2]Department of Medicine, Division of Endocrinology, University of Virginia, School of Medicine, Charlottesville, Virginia, USA

Email: Kathryn Dort - kar2b@virginia.edu; Shetal Padia - shp6a@virginia.edu; Brian Wispelwey - bw9g@virginia.edu; Christopher C Moore* - ccm3u@virginia.edu

* Corresponding author

Published: 8 June 2009

AIDS Research and Therapy 2009, 6:10 doi:10.1186/1742-6405-6-10

Received: 10 November 2008
Accepted: 8 June 2009

This article is available from: http://www.aidsrestherapy.com/content/6/1/10

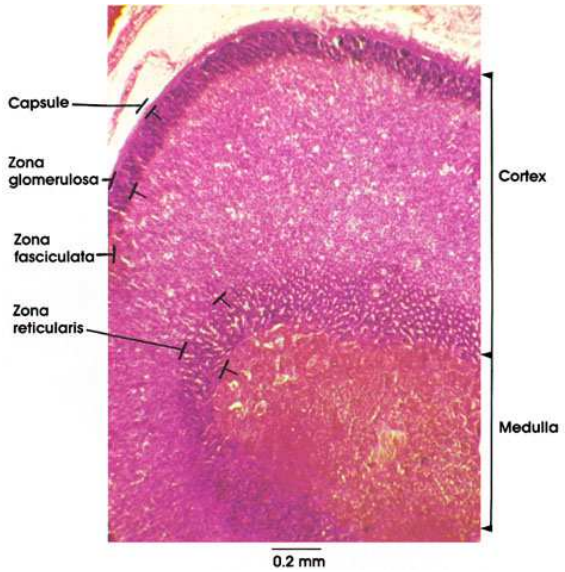
Abstract

Two HIV-1 infected patients developed signs and symptoms consistent with adrenal suppression after being exposed to intra-articular triamcinolone acetate while also receiving ritonavir as part of their highly active antiretroviral therapy. Laboratory evaluation confirmed secondary adrenal suppression in both cases. Both patients recovered without the need for chronic replacement steroids. Adrenal suppression has been described as an adverse outcome in patients treated with fluticasone and concomitant ritonavir. In the reported cases, the adrenal suppression likely developed as a result of increased systemic concentrations of triamcinolone due to an inhibition of cytochrome p450 3A4 metabolism. Practitioners of HIV medicine should be aware of the potential

Corticosteroid drug interactions with ritonavir			
	Steroid	Trade names	notes
Inhaled steroids	Fluticasone	Flixotide flixonase Seretide	✖
	Mometasone	Nasonex	✖
	Budesonide	Pulmicort Symbicort Rhinocort	✖
	Triamcinolone	Nasocort	✖
	Beclamethasone	Becotide	✔
Oral Steroids	Prednisolone		🡻
	Dexamethasone		✔
Injectable steroids *Intrarticular, im, epidural*	Triamcinolone	Kenalog	✖
	Depomedrone		✔

Iatrogenic adreno-cortical suppression

- When is steroid replacement needed?
- For how long?
- When is it safe to stop ?
- Any other investigations needed?
  - DEXA
  - HbA1c/GTT



11 whats the role of the HIV physician?

when safe to stop?
when is steroid replacement needed?
for how long?
Martin Mortgage, 08/11/2013

Case: outcome

- Remained on replacement steroids for 9 months
- Insulin discontinued after 6 months
- Proximal myopathy and osteoporosis persists
- Compensation settlement £ ?

12

what other things to test for?
HbAIc/OGTT
DEXA
etc……
Martin Mortgage, 08/11/2013

Learning points

TATT screen
Hypogonadism
Consider growth hormone deficiency
Performance enhancing/recreational drugs
Serious drug drug interactions with corticosteroids and ritonavir
Education of patients and non HIV prescribers
Co-manage complex patients with endocrinology

Acknowledgements

- The patients
- Prof Martin Fisher & Dr Daniel Richardson

Question

- In a population at risk of Diabetes what is the best method of screening?

- Random glucose or annual HbA1c ?

Ritonavir – drug interactions

- Highly potent inhibitor of Cytochrome P450 3A4

- Inhaled fluticasone:
  - Bioavailability 0.51%
  - Metabolised by CYP 3A4 in gut mucosa
  - 200-800 µg nasally produces plasma levels of <50 pg/ml
  - 3 patients on ritonavir and fluticasone
  - Levels 604, 299, 77 pg/ml