



48 year old male with abnormal thyroid function tests and HIV

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THE UNIVERSITY OF
CHICAGO
MEDICINE

HPI:

- 48 y.o. male with a hx of HIV on HAART presents with c/o nausea, vomiting and testicular pain for 2 weeks.
- Pain has radiation to left flank, no penile lesions or discharge.

Review of systems:

- Weight loss 30lbs in the last 6 months
- + Nausea, vomiting
- - diarrhea or abdominal pain
- + testicular pain
- + hair loss
- The pt reported compliance with his meds

Medications:

- Emtriva 200 mg daily
- Tenofovir 300 mg daily
- Ritonavir 100 mg BID
- Atazanavir 300 mg daily

Physical exam:

- Vitals: BP 127/69, Pulse 89, Resp 18, SpO2 96%, Wt 53.4 kg, BMI 17.
- Constitutional: Patient appears well-developed, well-nourished, not in acute distress.
- Eyes: Conjunctivae are not injected. Sclerae anicteric. Pupils are equal, round, and reactive to light. Extraocular movements are intact.
- ENT: Mucous membranes moist. **Warts on lips.**
- Neck: Palpable thyroid, not enlarged, no nodules.
- Lymph nodes: **Bilateral axillary lymphadenopathy. L groin lymph node.**
- Cardiovascular: Regular rate. Intact distal pulses.
- Respiratory/Chest: No wheezing, no rhonchi or crackles.
- Gastrointestinal/Abdomen: Soft, nontender, BS+. **Hepatomegaly, splenomegaly.**
- Genitourinary: Right testis shows no mass, no swelling and no tenderness. **Left testis shows tenderness.**
- Neurological: AAOx3.

CT:



- Hepatomegaly
- Splenomegaly
- Multiple enlarged lymph nodes in the chest, abdomen, and pelvis

Labs:

| | | | |
|-----|----|-----|-----|
| 130 | 99 | 21 | 129 |
| 4.0 | 19 | 1.1 | |

Ca 8.4 (8.4-10.2 mg/dL),
Phos 2.8 (2.5-4.4 mg/dL)
Mg 1.5 (1.6-2.5 mg/dL)

LFTs:

Total Protein 6.8 (6-8.3 g/dL)
Albumin 2.9 (3.5-6 g/dL)
Total Bilirubin 1.3 (0.1-1 mg/dL)
Bilirubin, conjugated 0.4 (0-0.3 mg/dL)
Alk Phos 366 (30-120 U/L)
AST 24 (8-37 U/L)
ALT 24 (8-35 U/L)

8AM cortisol 14.8 mcg/dL

| | | |
|-----|------|----|
| 7.9 | 8.1 | 88 |
| | 24.1 | |

HIV viral load 8981 copies/mL
CD4 count 136.7 (515 - 1642 /UL)

Chlamidia/GC probe (urine): negative

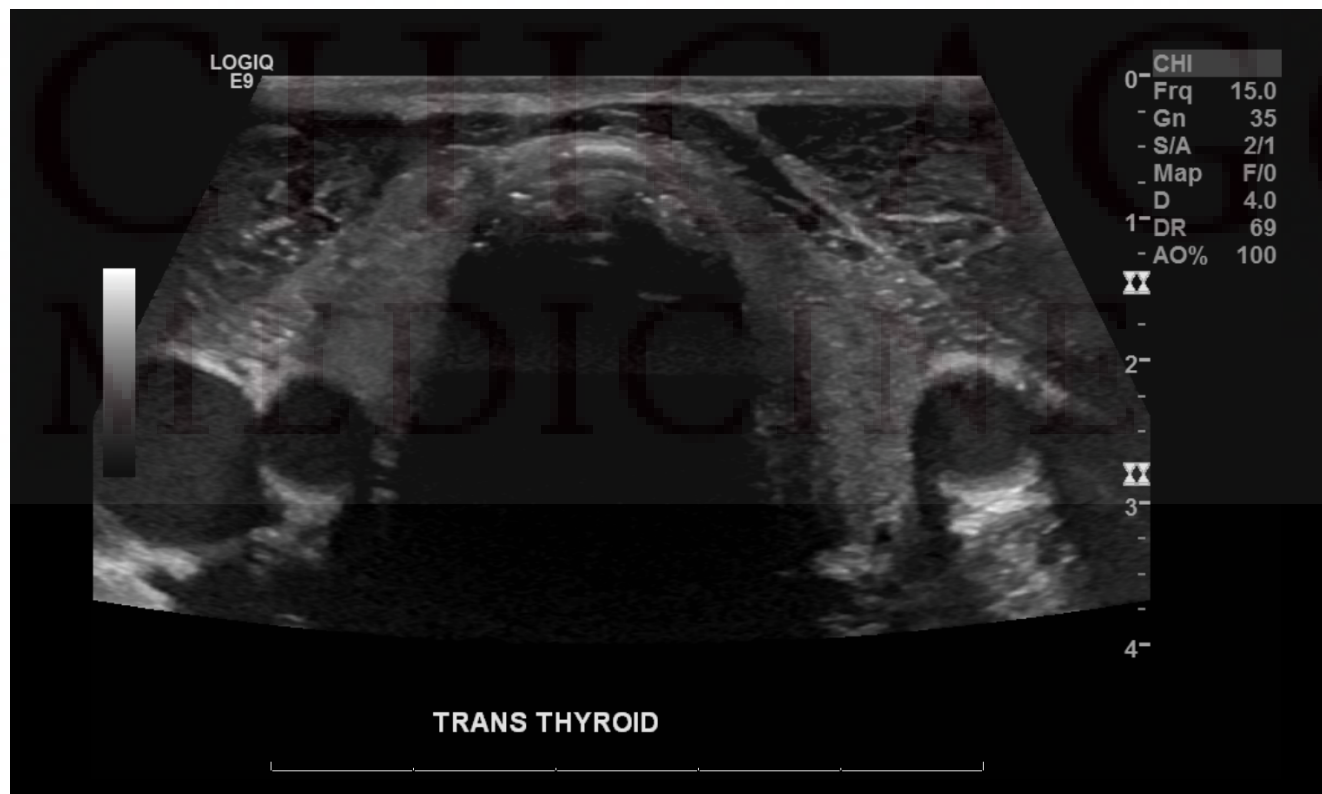
CMV, EBV DNA (blood): negative
Cryptococcal AG (blood): negative
Blastomyces AB (blood): negative
Bartonella IgM and IgG: negative
Respiratory panel (nasal swab): negative
Quantiferon TB-gold: negative
S. Pneumoniae AG (urine): negative
Toxoplasma IgG: negative
RPR: negative
C.diff, ova and parasites: negative

Urin cx, blood cx, stool cx: negative

- The primary team noted that the pt had elevated TSH 5.89 from 06/2013, therefore TFTs were obtained
- TSH 0.01, FT4 3.46, TT3 159,
- TSI neg, TPO Ab neg, TSH receptor Ab neg

Thyroid US:


- Unremarkable thyroid US without nodules or evidence of acute thyroiditis.




TFTs:

| | Ref. Range | 1/7/2014 | 1/8/2014 | 1/9/2014 | 1/10/2014 |
|------------------|--------------------------------|-----------|-----------|----------|-----------|
| | | 15:02 | 08:41 | 04:54 | 04:56 |
| Thyroxine, Free | Latest Range: 0.9-1.7 ng/dL | 2.97 (H) | 2.49 (H) | 2.12 (H) | 1.85 (H) |
| Thyrotropin | Latest Range: 0.30-4.00 mcU/mL | <0.01 (L) | <0.01 (L) | | |
| Triiodothyronine | Latest Range: 80-195 ng/dL | | 114 | 96 | |


- The pt underwent excisional biopsy of L groin lymph node
- Bacterial, fungal Cx, AFB stain were negative. Histopathology was consistent with HIV lymphadenopathy
- Treated with doxycycline 100 mg q12h x 10 days for orchitis (although it was most likely viral)
- Started on Bactrim SS daily for prophylaxis
- The pt was instructed to follow up with Cook County for repeat TFTs in 2 weeks after the discharge

- 
- 04/2014
 - The pt presents with cough, nausea, vomiting and diarrhea for 3 days
 - Reports extreme fatigue and weakness, no energy

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- TFTs were rechecked:
 - TSH 96.4, FT4 <0.1, TT3 <20, Tg Ab > 30, anti TPO Ab 30.
 - The pt was started on LT4 75mcg/day

TFTs:

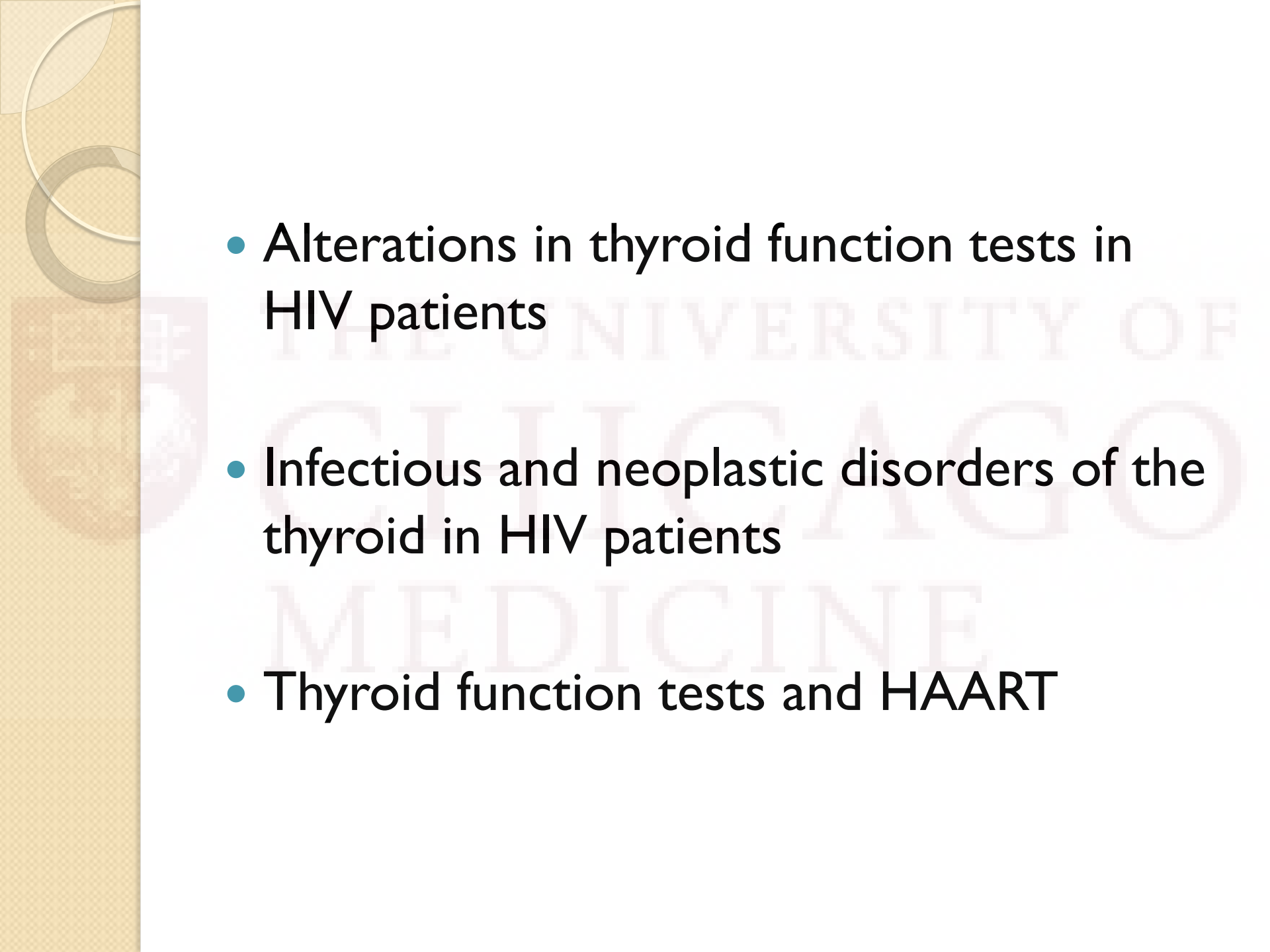
| | Ref. Range | 4/8/2014 19:54 | 4/17/2014 04:18 |
|------------------|--------------------------------|----------------|-----------------|
| Thyroxine, Free | Latest Range: 0.9-1.7 ng/dL | <0.10 (L) | 0.22 (L) |
| Thyrotropin | Latest Range: 0.30-4.00 mcU/mL | 96.40 (H) | 129.30 (H) |
| Triiodothyronine | Latest Range: 80-195 ng/dL | <20 (L) | |
| LT4 dose | | 75mcg/day | 150mcg/day |


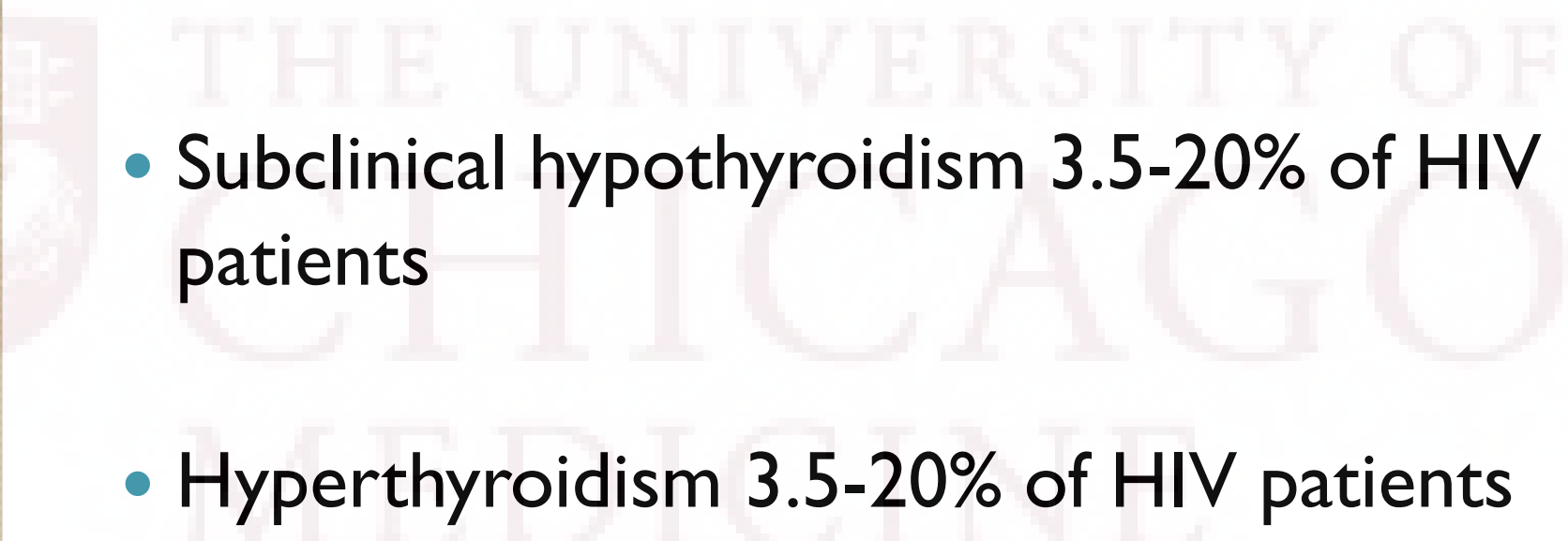
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- The pt was treated for CAP with azithromycin and ceftriaxone for 7 days, Bactrim DS TID 21 days for poss PCP
 - All infectious work up for diarrhea was negative, treated with Imodium, diarrhea resolved prior to discharge
 - The pt was scheduled for a follow up with endocrinology




05/2014

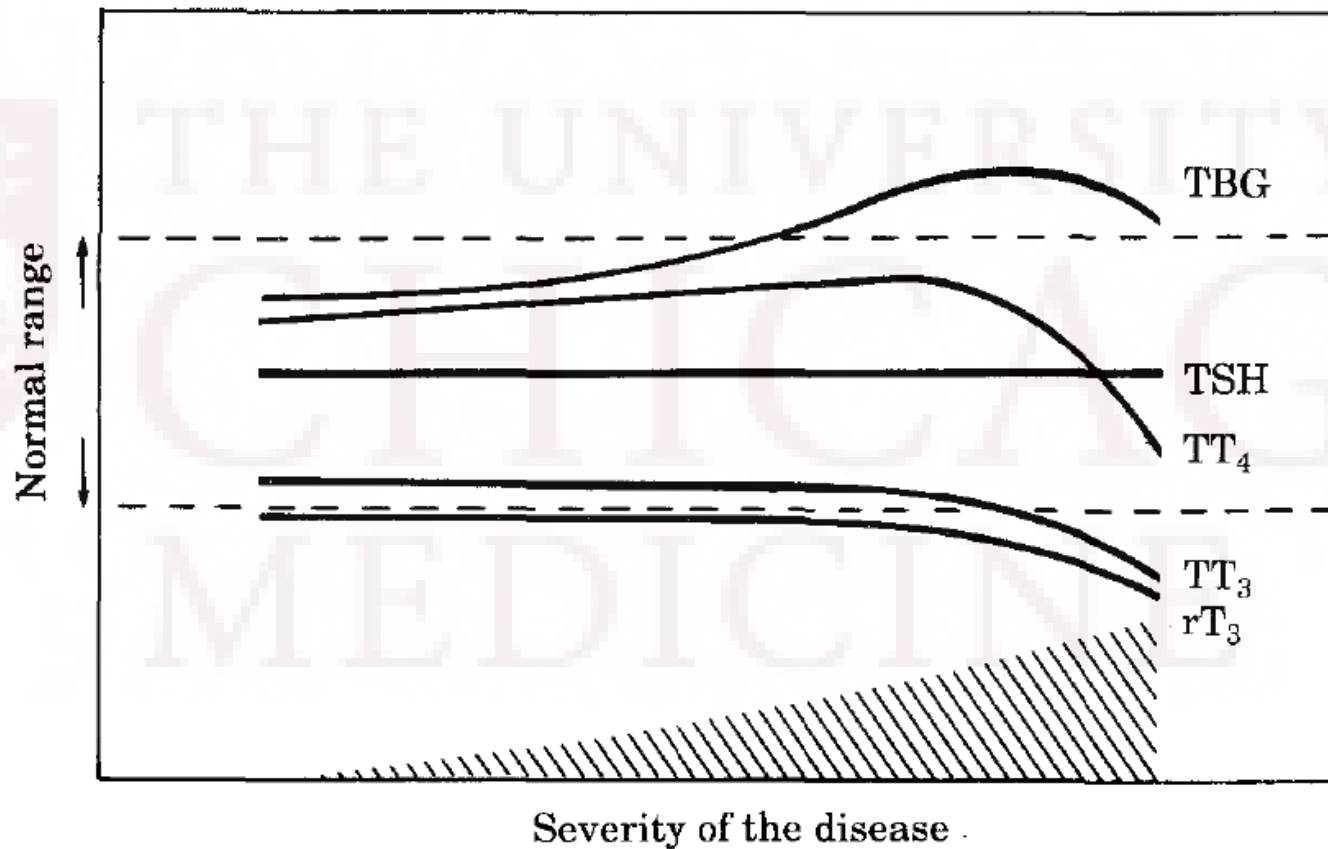
- TSH 98.95, FT4 0.13
- Reports noncompliance with medications
- Requested to be seen by hospice

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- Alterations in thyroid function tests in HIV patients
 - Infectious and neoplastic disorders of the thyroid in HIV patients
 - Thyroid function tests and HAART

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- Hypothyroidism 1-2.5% of HIV patients
 - Subclinical hypothyroidism 3.5-20% of HIV patients
 - Hyperthyroidism 3.5-20% of HIV patients
 - Subclinical hyperthyroidism <1%

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- One of the most characteristic findings is an elevation of TBG, which is associated with progression of HIV infection
 - There is a decline in TT4, TT3, FT4 and FT3 with a progression of a disease
 - Decrease in T4 and T3 is seems to be due to decreased extra thyroidal conversion of T4 to T3 and increase in binding globulins

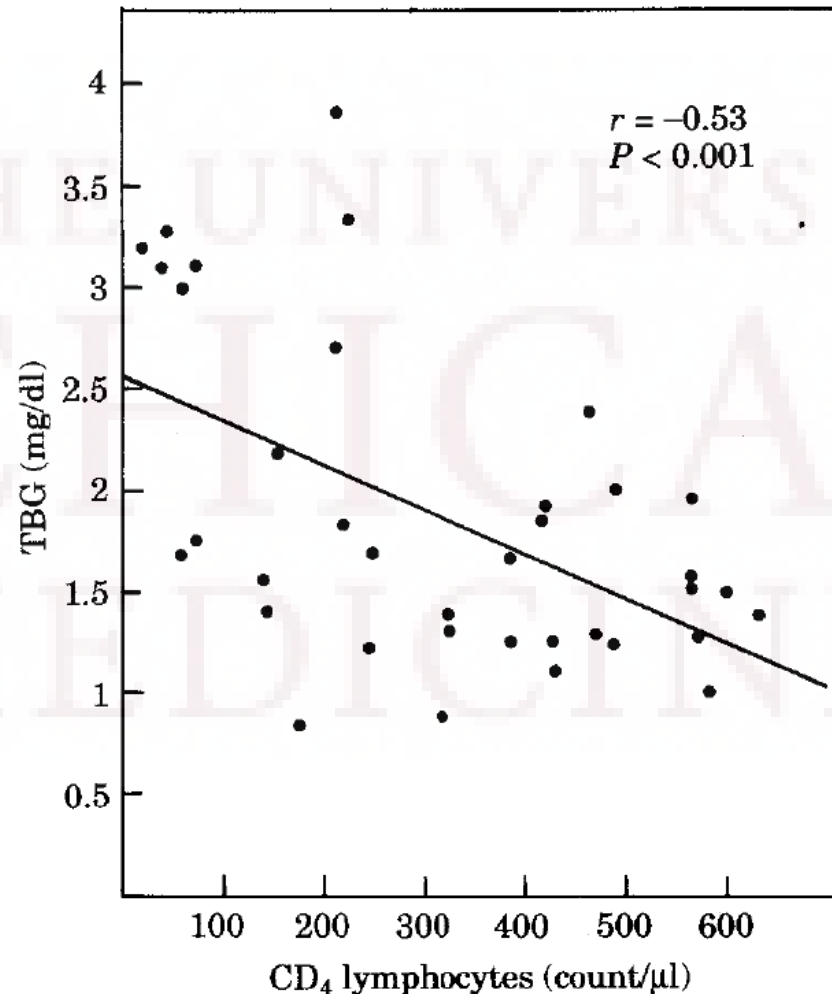
Thyroid function tests and HIV



TBG elevation in HIV:

- Increased liver synthesis and decreased degradation
- Isolated (CBG and SHBG are not increased)
- Correlate with a disease progression and CD4 count and was used as a surrogate marker of disease progression in the past

Correlation between TBG and CD4 count



Autoimmune thyroid disease in HIV patients:

TABLE 2. Characteristics of 17 HIV-Positive Patients Presenting With Thyroid Disease

| Patient* | Sex/ Age (yr) | Ethnicity | Endocrine Diagnosis | CDC Clinical Staging of HIV Disease | Nadir CD4 Cell Count (cells/mL ³) | Duration of Immune Reconstitution Before AITD (mo) | CD4 Cell Increment From Nadir to AITD (cells/mL ³) |
|----------|------------------|------------|------------------------------------------------|-------------------------------------------|-----------------------------------------------------|----------------------------------------------------------|-------------------------------------------------------------------------|
| 1 | F/38 | White | Graves | B | NK | NK | NK |
| 2 | F/35 | B. African | Graves | C | 73 | 29 | 116 |
| 3* | F/39 | B. African | Graves | B | 100 | 10 | 134 |
| 4 | M/37 | B. Carib | Graves | B | 10 | 23 | 453 |
| 5 | F/36 | B. African | Graves | C | 2 | 32 | 311 |
| 6 | F/41 | B. African | Graves, DM, LRS | B | 50 | 14 | 680 |
| 7 | F/47 | White | Graves | A | 107 | 9 | 44 |
| 8 | F/55 | B. African | Thyroiditis, hashitoxicosis, hypothyroid | C | 215 | 8 | 128 |
| 9 | F/32 | B. African | Graves | C | 10 | 25 | 670 |
| 10 | F/39 | B. African | Hypothyroid, LRS | A | 220 | 15 | 130 |
| 11 | F/32 | B. African | Graves | B | 5 | 16 | 459 |
| 12 | F/31 | B. African | Graves | C | 1 | 18 | 840 |
| 13* | F/38 | B. African | Graves, hypoadrenalism, DM | C | 1 | 9 | 390 |
| 14* | F/35 | B. African | Graves | C | 96 | 21 | 371 |
| 15* | M/49 | White | Graves | C | 7 | 28 | 270 |
| 16* | M/52 | Chinese | Graves, DM, LRS | C | 114 | 16 | 377 |
| 17* | F/41 | White | Graves | C | 54 | 33 | 279 |

Abbreviations: B. African = black African; B. Carib = black Caribbean; DM = type II diabetes mellitus; LRS = lipid redistribution syndrome; CDC = Centers for Disease Control; NK = not known.

*Asterisks indicates multi-HAART experienced patients, as described in Methods section. (The remaining patients were single-HAART experienced.)

Chen F, Day SL, Metcalfe RA, Sethi G, Kapembwa MS, Brook MG, Churchill D, de Ruiter A, Robinson S, Lacey CJ, Weetman AP. Characteristics of autoimmune thyroid disease occurring as a late complication of immune reconstitution in patients with advanced human immunodeficiency virus (HIV) disease. *Medicine* (Baltimore). 2005 Mar;84(2):98-106.

Autoimmune thyroid disease in HIV patients:

TABLE 4. Comparative Baseline HIV and Immune Reconstitution Data for AITD and Control Groups

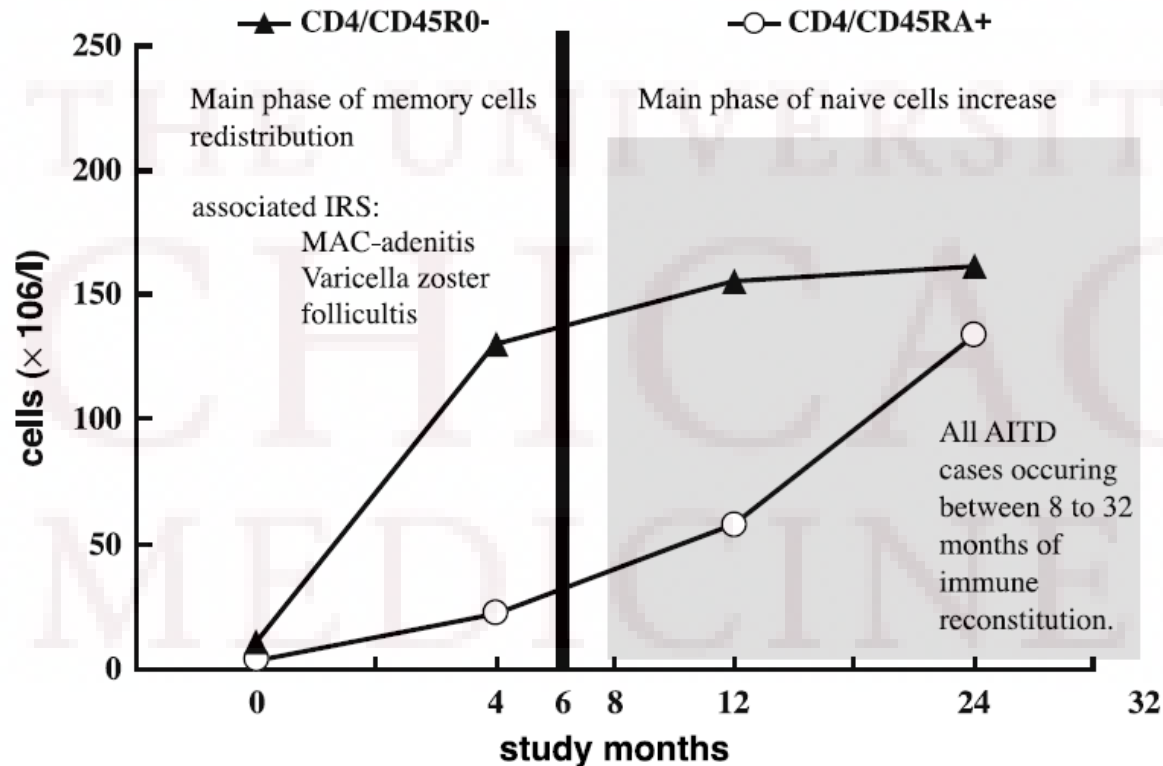
| Characteristic | | Group | | |
|----------------|--------------------------------------------------------------------------|-------------|-------------|---------------------------|
| | | Control | AITD | Total |
| Gender | Male | 21 (87.5%) | 3 (12.5%) | 24 (100%) |
| | Female | 53 (79.1%) | 14 (20.9%) | 67 (100%) |
| | Total | 74 (81.32%) | 17 (18.68%) | 91 (100%) |
| Mean | Age (yr) | 39.8 | 38.5 | |
| | Baseline CD4 count (cells/mL ³) | 218.8 | 66.6 | 95% CI, $p > t = 0.004$ |
| | Increase in CD4 count during observation period (cells/mL ³) | 199.6 | 355.1 | 95% CI, $p > t = 0.004$ |
| CDC stage | A | 37 | 2 | 39 |
| | B | 22 | 5 | 27 |
| | C | 15* | 10* | 25 |
| | Total | 74* | 17* | 91 |

95% CI, (Pearson chi-square = 12.1955, Pr = 0.002).

*15/74 versus 10/17.

Chen F, Day SL, Metcalfe RA, Sethi G, Kapembwa MS, Brook MG, Churchill D, de Ruiter A, Robinson S, Lacey CJ, Weetman AP. Characteristics of autoimmune thyroid disease occurring as a late complication of immune reconstitution in patients with advanced human immunodeficiency virus (HIV) disease. *Medicine* (Baltimore). 2005 Mar;84(2):98-106.

Autoimmune thyroid disease in HIV patients:



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Abnormal thyroid function and HAART:

TABLE 1. Treatments Patients With Thyroid Disease Were Receiving Compared With the Entire Clinical Cohort

| | Clinic Cohort N = 3500 | Abnormal Thyroid Function n = 54 | |
|-----------------------------|------------------------|----------------------------------|-----------------------------------|
| | | Hypothyroidism n = 28 (51.9%) | Hyperthyroidism n = 26 (48.1%) |
| Naive patients, N (%) | 656 (18.7) | 2 (7.1) | 3 (11.5) |
| Patients on PIs, N (%) | 765 (21.9) | 8 (28.6) | 12 (46.2), $P = 0.002$ |
| Patients on NNRTIs, N (%) | 1509 (43.1) | 16 (57.1), $P = 0.025$ | 7 (26.9) |
| EFV | — | 13 | 6 |
| NVP | — | 3 | 1 |
| Triple class regimen, N (%) | 385 (11.0) | 0 (0.0) | 1 (3.8) |

EFV, efavirenz; NVP, nevirapine; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Nelson M, Powles T, Zeitlin A, Sen P, Scourfield A, Bower M, Gazzard B, Stebbing J. Thyroid dysfunction and relationship to antiretroviral therapy in HIV-positive individuals in the HAART era. *J Acquir Immune Defic Syndr*. 2009 Jan 1;50(1):113-4.

Hypothyroidism and HAART:

Table 2 Results of logistic regression model of factors associated with overt hypothyroidism

| | Univariable results | | | Multivariable results | | |
|-------------------------------------------------|---------------------|------------|---------|-----------------------|------------|---------|
| | Odds ratio | 95% CI | P-value | Odds ratio | 95% CI | P-value |
| Nadir CD4 count (per 100 cells/ μ L higher) | 0.84 | 0.69, 1.01 | 0.07 | 0.97 | 0.78, 1.21 | 0.81 |
| Gender | | | | | | |
| Male | 1.00 | – | 0.009 | 1.00 | – | 0.11 |
| Female | 2.40 | 1.24, 4.62 | | 2.21 | 0.84, 5.85 | |
| Age (per 10 years older) | 1.39 | 0.99, 1.97 | 0.06 | 1.33 | 0.91, 1.95 | 0.14 |
| Risk group | | | | | | |
| Homosexual | 1.00 | – | 0.03 | 1.00 | – | 0.30 |
| Heterosexual | 1.95 | 0.99, 3.85 | | 1.26 | 0.47, 3.37 | |
| Other | 3.40 | 0.23, 9.46 | | 2.40 | 0.77, 7.43 | |
| AIDS diagnosis | | | | | | |
| Yes | 1.00 | – | 0.01 | 1.00 | – | 0.44 |
| No | 0.27 | 0.99 | | 0.74 | 0.35, 1.57 | |
| ART use | | | | | | |
| None | 0.42 | 0.18, 0.97 | 0.06 | 0.55 | 0.21, 1.44 | 0.30 |
| PI-based | 1.00 | – | | 1.00 | – | |
| NNRTI-based | 0.60 | 0.24, 1.52 | | 0.60 | 0.23, 1.52 | |
| Other | 1.34 | 0.56, 3.18 | | 1.29 | 0.54, 3.12 | |

The model excludes those with overt hyperthyroidism, and includes factors significant at the 5% level in Table 1.
ART, antiretroviral therapy; CI, confidence interval; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor.

Infectious and neoplastic disorders of the thyroid in HIV patients

- Autopsy of 100 AIDS patients prior to the era of HAART showed thyroid involvement with opportunistic infections:
- *Mycobacterium tuberculosis* 23%
- CMV 17%
- *Cryptococcus neoformans* 5%
- *Mycobacterium avium* 5%
- *Pneumocystis carinii* 4%
- Other bacteria and fungi 7%

Summary:

- Thyroid dysfunction is common in HIV infected patients
- One of the most characteristic findings is elevation of TBG, which correlate with CD4 and was used as a surrogate marker for disease severity in the past
- Hyperthyroidism is more common than hypothyroidism in HIV patients and most commonly due to Graves disease
- AITD could be linked to immune reconstitution syndrome
- Opportunistic infections can affect thyroid directly
- It could be a link between HAART medications and thyroid dysfunction but data is controversial

References:

- Lambert M. Thyroid dysfunction in HIV infection. *Baillieres Clin Endocrinol Metab.* 1994 Oct;8(4):825-35
- Chen F, Day SL, Metcalfe RA, Sethi G, Kapembwa MS, Brook MG, Churchill D, de Ruiter A, Robinson S, Lacey CJ, Weetman AP. Characteristics of autoimmune thyroid disease occurring as a late complication of immune reconstitution in patients with advanced human immunodeficiency virus (HIV) disease. *Medicine (Baltimore).* 2005 Mar;84(2):98-106.
- Nelson M, Powles T, Zeitlin A, Sen P, Scourfield A, Bower M, Gazzard B, Stebbing J. Thyroid dysfunction and relationship to antiretroviral therapy in HIV-positive individuals in the HAART era. *J Acquir Immune Defic Syndr.* 2009 Jan 1;50(1):113-4.
- Madge S, Smith CJ, Lampe FC, Thomas M, Johnson MA, Youle M, Vanderpump M. No association between HIV disease and its treatment and thyroid function. *HIV Med.* 2007 Jan;8(1):22-7.
- Basílio-De-Oliveira CA. Infectious and neoplastic disorders of the thyroid in AIDS patients: an autopsy study. *Braz J Infect Dis.* 2000 Apr;4(2):67-75.