Current Issues in the US:
Caring for the Patient beyond HIV Infection

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Case Outline

- **Anneliese H.**
  - **Diabetes**
  - **Hyperlipidemia**
  - **Antiretroviral selection**
- Teri A.
  - Coronary heart disease
  - Hepatitis C
  - Antiretroviral selection

Anneliese – Case Overview

- 42 year old heterosexual Caucasian female, Dx HIV+ 2002
- SH: Divorced female, lost custody of 3 children
  Recurrent adult cocaine use (rehab programs twice)
  History of childhood abuse
  2007 lost job and insurance
- FH: Diabetes, hypertension, bipolar disease,
  CAD (father MI at 60yr)
- PMH: Diabetes
  Hyperlipidemia
  Cervical dysplasia
  Depression with mood swings

Anneliese – Case Overview

- 3/2009: new to clinic – following 2 year off prescriptions
  - Sx: polyuria, polydipsia, 15lb wt loss, GERD, depression with mood swings, genital herpes
  - PE: BMI 27, Waist 91cm, BP 110/70

	2002-2007	3/2009
CD4 # / %	500s	**82 / 6%**
HIV-1 RNA	UD on ARV	122,000
ARV	TDF-FTC-ATVr	Off meds
Comments	1.5 year total ARV, Hx rash with EFV	GT negative
Other Results		Creat 0.81, Ur Prot neg TC 141 / **TGA 758 / HDL 26** Gluc 253 / **HgbA1c 9.6**

Anneliese – ?# 1

- Which of the following therapies need to be started urgently?

  1) Antiretroviral therapy
  2) OI prophylaxis
  3) Diabetes therapy
  4) Lipid lowering therapy
  5) Anti-depressants

  Check all that apply

Anneliese – ?# 1 Answer

- Most urgent treatments?

1) Initiation of antiretroviral therapy → Underlies ultimate treatment success
2) **Initiation of OI prophylaxis**
3) **Initiation of diabetes therapy**

} **Potential immediate complications**

4) Initiation of lipid lowering therapy → Confounded by high glucose, potential pancreatitis risk
5) Initiation of anti-depressants → May underlie ultimate treatment success

Anneliese – Case Follow-Up

- She was started initially on the following:
  - SMX-TMP 800/160mg – once daily
  - Metformin 500mg – twice daily
  - Gemfibrozil 600mg – twice daily
  - Acyclovir 400 mg – twice daily

  (all available through discount pharmacy program)

- Antiretrovirals not initially available due to lack of funding

Anneliese –?# 2

- At her follow-up appointment 2 months later she was tolerating the metformin and gemfibrozil, but her random glucose in clinic was 301. Which of the following would be your next step in treating her diabetes?

  1) Intensive dietary modification
  2) Increased metformin dose
  3) Metformin combined with a sulfonylurea or a thiazolinedione
  4) Short and long acting Insulin

  --- *Choose all that apply* ---

Anneliese –?# 2 Answer

- Which one of the following would be your next step in treating her diabetes?

1) Intensive dietary modification → Counseling done

2) Increased metformin dose → Increased to 850mg

3) Metformin combined with a sulfonylurea or a thiazolinedione → Glyburide added

4) Short and long acting Insulin

Anneliese – ?# 2 Discussion

- Diabetes treatment sequence:

Hgb A1c	Strategy	Medications
6-7	Monotherapy	Metformin, TZD, or sulfonylurea, or newer drug
7-8	Combination therapy	2 of the above
8-10	Intensified combination therapy	Increased doses Multi-class
>10	Insulin	Long and short-acting

Am.Assoc.Clin.Endocrin. , Endocrine Practice 2007, 13:3-68;
Am.Diab.Assoc., Diabetes Care 2010, 34:S11-S61.

Anneliese – ?# 2 Discussion

- Standard diabetes medications:

Medication	Advantages	Disadvantages / Risks
Metformin	↓ Insulin resistance No weight gain ↓ NASH, TGA, LDL	Risk lactic acidosis Caution with renal or hepatic impairment or unstable CHF
Thiazolidinedione	↓ Insulin resistance ↓ TGA, ↑ HDL ↑ Endothelial function	Weight gain Edema (not in CHF) Caution in hepatic impairment
Sulfonylurea	↑ Insulin secretion	Weight gain Hypoglycemia
Insulin	Effective after β-cell failure	Weight gain

Anneliese – ?# 2 Discussion

- Dietary recommendations:

Food Group	Diabetes	Hyperlipidemia
Fats: - Total - Saturated - Cholesterol	< 30% < 10% < 300 mg/d	25-35% < 7% (if high LDL) < 200 md/d
Soluble **Fiber**	25-50 g/d	≥ 10-25 g/d
Carbohydrates	"Low carbohydrate" whole grains, fruits/vegies	50-60% whole grains, fruits/vegies
Other	↓ Insulin resistance: - ↓ 500-1000 calories - 5-7% weight loss	↑plant sterols and stanols

(% of total daily calories)

Anneliese – ?# 3

- In July 2009 the patient was able to start ARVs. She reports an irregular eating schedule and problems with adherence. Which of the following 3rd ARV agents would be appropriate along with a 2-NRTI backbone?

  1) Atazanavir-ritonavir
  2) Darunavir-ritonavir
  3) Efavirenz
  4) Fosamprenavir-ritonavir
  5) Lopinavir-ritonavir

Anneliese – ?# 3

- 3rd ARV agents options:

1) Atazanavir-ritonavir
2) Darunavir-ritonavir
3) Efavirenz
4) **Fosamprenavir-ritonavir**
5) Lopinavir-ritonavir

- Antacid caution
- Dosing with food
- History of rash and mood disorder
- **Dosing without food**
- Higher rate ↑ TGA

Anneliese – Case Follow-Up

	3/2009	5/2009	7/2009	8/2009	1/2010
CD4 #	82 / 6%		--	71/10%	116/12%
HIV-1 RNA	122,000		--	212	<75
ARV	Off meds	None	ABC-3TC-FPVr	- Same	- Same
TC/TGA/HDL	141/ 758 /26		--	--	254 / 879 / 31
FBS/HgbA1c	253 / 9.6			318 / 8.1	269 / 7.7
Medications Start Dates	- Metformin 500 bid - Gemfibrozil 600 bid	- Metformin 850 bid - Glyburide 10mg daily - Same	- Same - Same - Same	- Same - Same - Same	

Anneliese – ?# 4

- The patient has achieved viral suppression with beginning immune recovery. What additional steps can be taken to control her glucose and lipids?

  1) Evaluate for secondary causes of dyslipidemia
  2) Add additional lipid reducing medications
  3) Add additional glucose reducing medications
  4) Reinforce lifestyle changes of diet and exercise
  5) Change antiretroviral regimen

  --- check all that apply ---

Anneliese – ?# 4 Answer

- The patient has achieved viral suppression with beginning immune recovery. What additional steps can be taken to control her glucose and lipids?

1) Evaluate for secondary causes of dyslipidemia

2) Add additional lipid reducing medications

3) Add additional glucose reducing medications

4) Reinforce lifestyle changes of diet and exercise

5) Change antiretroviral regimen --- *also an option*

Anneliese – ?#4 Discussion

- Secondary causes of hypertriglyceridemia:
  - Diseases: hyperglycemia , chronic kidney disease, HIV
  - Lifestyle: alcohol, smoking, inactivity, high carbohydrate diet, overweight
  - Drugs: estrogens, thiazides, β-blockers, steroids, protease inhibitors
- Additional treatments for hypertriglyceridemia:
  - Niacin: problematic side effect of hyperglycemia
  - Omega 3: additional cardio-protective benefit
  - Statins: anti-inflammatory and cardio-protective benefit

Anneliese – Case Follow-Up

- The patient returns after 10 month absence from clinic due to loss of insurance. She's treated for candida vaginitis.

	3/2009	7/2009	1/2010	**12/2010**
CD4 #	82 / 6%		116/12%	**24/5%**
HIV-1 RNA	122,000		<75	26,053
ARV	Off meds	ABC-3TC-FPVr	Same	Off meds
TC/ TGA/ HDL/ LDL	141/ 758 / 26/ --		254 / 879 / 31/ --	278/ **1904**/ 27/ --
FBS/HgbA1c	253 / 9.6		269 / 7.7	334 / **11.8**
Meds	-Met.500[2] -Gem.600[2]	-Met.850[2] -Glyb. 10[1] -Gem.600[2]	Same Same Same	Off meds

Anneliese – ?# 5

- In addition to providing OI prophylaxis and restarting gemfibrozil, how would you manage her ARVs and DM medications at this time?

  1) Resume prior ARVs and oral diabetes regimen
  2) Resume prior meds and add insulin
  3) Start new ARV regimen while resuming her prior oral diabetes regimen
  4) Start new ARV regimen, resume her prior oral diabetes regimen and add insulin

Anneliese – ?# 5 Answer

- In addition to providing OI prophylaxis and restarting gemfibrozil, how would you manage her ARVs and DM medications at this time?

1) **Resume prior ARVs and oral diabetes regimen**
2) Resume prior meds and add insulin
3) Start new ARV regimen while resuming her prior oral diabetes regimen
4) Start new ARV regimen, resume her prior oral diabetes regimen and add insulin

Anneliese H – Case Follow-Up

	3/2009	7/2009	1/2010	12/2010	3/2011
CD4 #	82 / 6%		116/12%	24/5%	37/7%
HIV-1 RNA	122,000		<75	26,053	423
ARV	Off meds	ABC-3TC-FPVr	Same	Off meds	ABC-3TC-FPVr
TC/ TGA/ HDL/ LDL	141/ 758 / 26/ --		254 / 879 / 31/ --	278/ 1904/ 27 / --	265/ **486**/ 31/ 132
FBS/HgbA1c	253 / 9.6		269 / 7.7	334 / 11.8	302 / **10.6**
Meds	-Met.500[2] -Gem.600[2]	-Met.850[2] -Glyb. 10[1] -Gem.600[2]	Same Same Same	Off meds	-Met.850[2] -Glyb. 10[1] -Gem.600[2]

Anneliese – ?# 6

- Her HIV and lipid status show good initial improvement but her diabetes remains poorly controlled. What additional step/s would you take to control her diabetes?

1) Increase dose of metformin
2) Add thiazolidinedione
3) Add "post-prandial" newer agent
4) Change to combined short and long-acting insulin regimen
5) Add thiazolidinedione and long-acting insulin

Anneliese – ?# 6 Answer

- Additional step/s to control her diabetes?

1) Increase dose of metformin → Insufficient
2) Add thiazolidinedione → Option
3) Add "post-prandial" newer agent → Need home glucose testing
4) Change to combined short and long-acting insulin regimen → Difficult adherence
5) **Long-acting insulin** → **Insulin recommended @ HgbA1c >10**

Anneliese – ?#6 Discussion

- Current insulin recommendations (**HgbA1c >10**):
  - Long-acting basal (Lantus, Levemir or NPH) ---***plus***---
  - Rapid acting synthetics (Aspart, Lispro, Glulisoline)

INSULINS	Onset	Peak	Dur'n
Aspart (NovoLog) **Lispro (Humalog)** **Glulisine (Apidra)**	5-15m	30-90m	<5h
Regular	30-60m	2-3h	5-8h
NPH	2-4h	4-10h	10-16h
Glargine (Lantus)	2-4h	No peak	20-24h
Detemir (Levemir)	3-8h	No peak	6-23h

Anneliese – ?#6 Discussion

- Newer diabetes medications:
  - ↓Post-prandial glucose (↓ microvascular complications):
    - Glinides + erratic eating schedules
      - Renal or hepatic impairment, $$
    - α-Glucosidase inhibitors - GI side effects; glucose tablets for rescue
      - Renal or hepatic impairment
    - Sitagliptan + weight loss
      - diarrhea, $$
  - ↓ Gastric empyting (↑satiety):
    - Exentatide + no weight gain, minimal hypoglycemia
    - Pramlinitide + weight loss, - injectable with insulin, $$

Anneliese H – Case Follow-Up

	3/2009	7/2009	1/2010	12/2010	3/2011	6/2011
CD4 #	82 / 6%		116/12%	24/5%	37/7%	58/8%
HIV-1 RNA	122,000		<75	26,053	423	**<40**
ARV	Off meds	ABC-3TC-FPVr	Same	Off meds	ABC-3TC-FPVr	Same
TC/ TGA/ HDL/ LDL	141/ 758 / 26/ --		254 / 879 / 31/ --	278/1904 /27	265/ 486/ 31/ 132	312/ **502**/ 35/ **166**
FBS/HgbA1c	253 / 9.6		269 / 7.7	334 / 11.8	302 / 10.6	87 / **7.1**
Meds	-Met.500[2] -Gem.600[2]	-Met.850[2] -Glyb. 10[1] -Gem.600[2]	Same Same Same	Off meds	-Met.850[2] -Glyb. 10[1] -Gem.600[2] -Lantus HS	Same Same Same Same

Case Outline

- Anneliese H.
  - Diabetes
  - Hyperlipidemia
  - Antiretroviral selection
- **Teri A.**
  - **Coronary heart disease**
  - **Hepatitis C**
  - **Antiretroviral selection**

Teri A – Case Overview

- 53 year old Caucasian heterosexual female
- Hospitalized for MI and Diagnosed HIV+ and HCV+ 8/2010
  - Tested due to thrombocytopenia and transaminitis in context of risk history
  - HIV- in 2000, never tested for HCV
  - HCV source: ex-partner (2002-2009)
  - HIV source unknown
- Risk factors: past hx of drugs and prostitution

Teri A – Case Overview

- No medical care prior to moving to AZ in 4/2010
- PMH: Post-menopausal since 2002
  Shingles in 1/2010
  STDs and PID, G6 P1 (CSxn) SAb 2 TAb 3
- SH: Cocaine and methamphetamine 1984-2002
  Prostitution 1995-2003
  Smoking: 30 pack-years
  Childhood sexual abuse by father
- FH: Mother with colon cancer
  Paternal grandfather died of MI in 60s
  Father alcoholic

Teri A – CAD Overview

- 8/2010 hospitalized for acute MI:
  - Left sided chest heaviness, at rest while smoking first cigarette of the morning, accompanied by diaphoresis and SOB
  - EKG: bradycardia (HR=50) with T-wave inversions and ST depression in anterolateral chest leads
  - Successive Troponin-I elevation:

Time (hr):	1 hr	5 hrs	8 hrs	18 hs	21 hrs
(NL <0.06)	0.05	1.05	1.81	4.68	5.06

Teri A – CAD Overview

- Only prior symptom was SOBOE with bicycle riding
- Sx resolved in ED with nitropaste, aspirin, integrilin (platelet inhibitor), lovenox, and metoprolol
- Cath lab:
  - LAD 40% occlusive lesion midvessel
  - RCA 50% occlusive proximal lesion, plus near complete occlusion distal vessel
- Tx: Extraction thrombectomy with percutaneous transluminal coronary angioplasty distal RCA

Teri A – CAD Overview

- Echocardiogram:
  - No regional wall abnormalities
  - Severe left atrial enlargement with moderately-severe diastolic dysfunction
  - Mild pulmonary hypertension
  - Preserved LV systolic function
  - Normal valves with mild mitral regurgitation
- Patient was discharged from the hospital

Teri – CAD ?#1

- In the HIV clinic, management of her coronary artery disease should include treatment with all the following EXCEPT?
  1) Alpha-blockers
  2) Beta-blockers
  3) ACE inhibitors
  4) Aspirin
  5) Statins
  6) Omega 3

Teri – CAD ?#1 Answer

- <u>Management of her coronary artery disease</u> should include treatment with all the following EXCEPT?

1) Alpha-blockers:	**no CAD benefit**
2) Beta-blockers:	improved CVD outcome post MI
3) ACE inhibitors:	↑ Nitric Oxide, improved CVD outcome post MI
4) Aspirin:	inhibits platelet aggregation
5) Statins:	↑ Nitric Oxide, ↓ LDL
6) Omega 3:	↑ endothelial function, ↑ HDL

Teri – CAD ?#1 Discussion

- General CAD management:
  - Beta-blockers — goal HR 50-60
  - ACE inhibitors — expect 20-30% ↑ creatinine via ↓ intraglomerular pressure
  - Aspirin — 81-325 mg daily
  - Statins — 1° goal LDL <70-100
  - Omega 3 — 2° goal HDL >40
  - Exercise — ↑ Nitric Oxide
  - Smoking cessation — ↓ vasospasm, atherogenesis, etc
  - Depression — 15-20% post MI incidence independent predictor mortallity

Teri – CAD Case Discussion

- CAD follow-up:
  - Treated with:
    - Metoprolol 25 mg twice daily
    - Aspirin 81 mg daily
    - Lisinopril 2.5 mg daily
    - Omega 3 capsules 1000 mg twice daily
  - Repeatedly encouraged to stop smoking
  - Encouraged to exercise
    - Limited by SOBOE and fatigue (HCV and anemia)
  - Atorvastatin was deferred during HCV treatment

Teri – ARV ?#2

- In the context of CAD and HCV infection which of one of the following antiretroviral medications does NOT have possible reasons to AVOID its usage?

  1) Abacavir
  2) Efavirenz
  3) Lopinavir
  4) Raltegravir
  5) Ritonavir
  6) Tenofovir

Teri – ARV ?#2 Answer

- In the context of CAD and HCV infection which of one of the following antiretroviral medications does NOT have possible reasons to AVOID its usage?

1) Abacavir — cohort "signal" of MI association
2) Efavirenz — risk of hyperlipidemia
3) Lopinavir — cohort "signal" of MI association
4) **Raltegravir**
5) Ritonavir — risk of hyperlipidemia
6) Tenofovir — risk of nephrotoxicity (HCV & renal atrophy)

Teri – Antiretroviral Treatment

- Baseline: GT neg, HLA B*5701 neg
- ARV: 3TC-ETV-RAL started 10/2010

	9/23/2010	11/4/2010	3/10/2011
WBC	3500	4300	5200
Lymphocyte	1200	1900	2400
CD4 Cell abs	257	345	426
CD4 % Helper T Cell	21	22	23
CD4/CD8 Ratio	0.3	0.3	0.4
HIV-1 RNA Quant	11813 (H)	<75	NOT DET

Teri – HCV ?#3

- In the context of her CAD infection how would you manage her hepatitis C infection?
  1) Avoid peg-interferon and ribavirin for one year following the MI due to risk of anemia
  2) Evaluate and treat the HCV whenever the patient is stable and ready
  3) Avoid peg-interferon and ribavirin entirely due to medication toxicity
  4) Consider HCV treatment only if starts to develop significant liver fibrosis

Teri – HCV ?#3 Answer

- In the context of her CAD infection how would you manage her hepatitis C infection?

  1) Avoid for one year due to anemia:
     diligently manage, but not contraindication
  2) **Evaluate and treat the HCV whenever the patient is stable and ready**
  3) Avoid entirely: *no cardio-toxicity*
  4) Only if significant liver fibrosis: *not required to wait*

Teri – HCV ?#4

- Which of the following factors are NOT prognostic of her response to HCV treatment?

1) Fasting glucose
2) HCV genotype
3) HCV quantitative RNA
4) Routine liver ultrasound
5) Liver biopsy

Teri – HCV ?#4 Answer

- Which of the following parameters will NOT affect her response to HCV treatment?

	Associated with Poorer Response:
1) Fasting glucose	▪ Insulin resistance
2) HCV genotype	▪GT 1
3) HCV quant. RNA	▪High
4) Routine Liver ultrasound	▪**Not applicable**
5) Liver biopsy	▪Bridging fibrosis

Teri A – HCV Staging Results

- Abdominal ultrasound 12/2010:
  - Hepatosplenomegaly with 1.5 cm liver lesion
  - Left renal atrophy (7.7cm length vs 12.4 cm / right)
  - No ascites
- Abdominal CT 1/2011:
  - Hepatic nodularity, isolated hemangioma
  - Left renal cortical scarring
- Liver needle core biopsy 3/2011:
  - Moderate portal, periportal and lobular inflammation
  - Stage 2-3 portal fibrosis with occasional bridging fibrosis

Teri – HCV ?#4 Discussion

Prognostic factors		Positive Predictors of Success
Age	53 years	No
BMI	23	**Yes**
Genotype	3a	**Yes**
HCV RNA	2,186,720	No
Fibrosis	Partial bridging	No/Yes
Glucose	93	**Yes**
CD4	After ARV = 426	**Yes**
HIV RNA	After ARV = <40	**Yes**
Drugs/EtOH	No	**Yes**
Psych	No	**Yes**

Teri – ARV Treatment Follow-Up

- HIV treatment: 3TC-ETV-RAL since 10/2010
- HCV treatment: RBV-PegIFNα2a since 5/2/2011

	9/23/2010	11/4/2010	3/10/2011	6/6/2011	8/31/2011
CD4 T Cell Abs	257	345	426	348	**250**
CD4 % Helper T Cell	21	22	23	31	46
CD4/CD8 Ratio	0.3	0.3	0.4	0.6	1.1
HIV-1 RNA Quant	11813 (H)	<75	NOT DET	NOT DET	NOT DET
Hep C RNA Quantitative, bDNA	--	2,186,720	--	18,992	<5

Screening for Non-Infectious Co-Morbidities

Adapted from EACS Guidelines October 2011

http://www.europeanaidsclinicalsociety.org/

Disease	Assessment	Follow-Up Frequency	Comments
CVD	• Risk assessment		Framingham score
	• EKG	Conditional	Consider prior to PI with potential conduction problems
HTN	• Blood pressure	Annual	
Lipids	• TC, HDL, LDL, TG	Annual	Repeat fasting prior to medical intervention
Diabetes	• Fasting plasma glucose	6-12 m	
	• HgbA1c or oral GTT	Conditional	if fasting glucose > 100-125 mg/dl (5.7-6.9 mmol/L)
Renal	• Risk assessment	Annual	CKD, DM, HTN, CVD, HCV, medications, family history
	• eGFR	3-12 m	More often if: CKD or risk factors present; or if on nephrotoxic drugs (ARV: TDF, IDV, ATV; OI: ganciclovir, amphoterocin; etc.)
	• Urine dipstick: protein, blood	6-12 m	Every 6 mo if eGFR <60 ml/min
	• Spot urine Prot:Creat	Conditional	If proteinuria ≥1+ or eGFR <60 ml/min
Bone	• Calcium, PO4, AlkPhos	6-12 m	
	• Risk assessment	2 y	FRAX score in patients >40 yr
	• DXA scan	Conditional	In at-risk patients
	• 25OH Vit D	Conditional	In at-risk patients: malabsorption, PO4 wasting, dark skin, CKD, dietary deficiency, lack of sunlight exposure

Screening for Non-Infectious Co-Morbidities

- Continued

Disease	Assessment	Follow-Up Frequency	Comments
Liver	• Risk assessment	Annual	More frequent on hepatotoxic drugs
	• ALT/AST, AlkPhos, Bilirubin	3-12 m	
NeuroCog	• Screening questions	2 yrs	Rule out confounding conditions
Depression	• Screening questions	1-2 yrs	More frequent in at-risk patients
Cancer	• Mammography	1-3 yrs	W: 50-70 yrs or W/M: high risk history
	• Cervical Pap • Colposcopy	1-3 yrs	W: Sexually active For ≥ ASCUS Pap
	• DRE and Anal Pap • Anoscopy	1-3 yrs	MSM: evidence preliminary M/W: high risk (HPV dis or RAI) For ≥ ASCUS Pap
	• Ultrasound and AFP	6 mo	Patients with cirrhosis – from any cause
	• DRE ± PSA	1-3 yrs	M >50, or high risk
	• FOBT or • Colonoscopy	1-3 yrs 5-10 yrs	50-75 yrs, or high risk