

Clinical Pearls and Perils: Short Cases and Clinical Questions

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December, 2007
Positive Health Program at Ward 86,
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Objectives

- To appreciate the richness of everyday clinical interactions and questions that arise.
- Look at some new drug interactions and newly appreciated HIV codon mutations
- Think about differential diagnoses by including social and cultural factors.

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- To cross or not to cross
- Read the fine print
- The Achilles heel
- Dizziness in urgent care
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- How do you spell relief
- Ratio inversion
- Tough pill to swallow
- Swollen face
- Asleep in SW
- Malaria and HIV?
- Won't take his pills

Strange Bedfellows

- I did an routine screening anal pap and std swabs in my patient who is a 46 y/o man, originally from Nicaragua, last trip there was 3 years ago.
- He was feeling fine, no GI complaints.
- His current CD4 was 507, VL < 75, he is on HAART.
- PMHx he had CNS toxo in the 1990's. His nadir CD4 was less than 10.
- He has sex with other HIV + men and usually uses condoms, but not always.

Unusual Anal PAP Result

- I was called by the pathology attending, the pap was wnl, but had an unusual finding.
- Cytotech: Source of Specimen(s) FINAL CYTOLOGIC DIAGNOSIS, Anal Thin Prep: Negative for Intraepithelial Lesion or Malignancy. Satisfactory for evaluation. No rectal columnar cells and/or metaplastic cells noted. Additionally, ***parasitic larvae consistent with either hookworm or strongyloides are present. Favored is strongyloides.*** Dr Wlodarczyk is informed.

Strongyloides



Questions for your consideration

- How would you manage this problem?
- Would you treat him and why or why not?
- Is he at risk for a disseminated infection?
- Is this a potential STD?

Strongyloides

- Even though he was asymptomatic, I treated him with Ivermectin at 0.2 mg/kg per day for 2 days.
- I treated him to prevent a worsening of his infection and to eliminate the chance of disseminated disease/hyperinfection in the future, should he need to be on immunosuppressants, like prednisone, or if his immune status would worsen.
- I found more than 1 reference that this could be a sexually transmitted disease.
- His repeat O+P 2 weeks later was negative for strongyloides.

More Strongyloides

- Strongyloides can complete its entire life cycle within the host and cause autoinfection. Larvae can re-enter the body through the skin, often the perianal area, or colonic mucosa.
- Strongyloides stercoralis may produce a cutaneous reaction when larvae penetrate the skin. The buttocks are commonly affected in chronic infection. The rash is called "**larva currens**" and is a serpiginous, raised, erythematous track and maybe severely pruritic. Those larvae could enter another person through their skin or mucosa (anal/rectal or oral) and cause an infection.
- Also, an immune reconstitution syndrome has been noted).

Larva Currens



More Strongyloides

- *Strongyloides stercoralis*. Capable of multiplying within the human. Possible severe strongy ass with HIV in tropics
- Hyperinfection syndrome: massive upregulation of autoinfection which produces large numbers of larvae which disseminate to lungs, liver, penetrate GI tract.
- Clinical course dominated by gram neg. sepsis, meningitis, pneumonia. Mortality 40-80%
- Recent study showed that HIV immunosuppression decreased infectious larvae in the gut. It proves an explanation for IRIS leading to hyperinfection
- Hyperinfection is also ass. With steroid use, wasting, and HTLV-1 inf. and HIV immunosuppression (CD4 mean of 90 in one series).

* Interesting fact: Posey D. High prevalence and presumptive treatment of schistosomiasis and strongyloides among African refugees. CID 2007;45:1310-5. Among refugees from Sudan (lost boys and girls) 44% and 46% respectively and Somali(Bantu) 73% and 23% who have resettled in the US.

Key Points on Strongyloides Case

- Getting this unusual pap report lead me to consider and learn about the following questions
- How would you manage this problem? Answer treat with Ivermectin and repeat O+P post rx
- Would you treat him and why or why not? Answer: to prevent the chance of future hyperinfection or disseminated disease, should he become more immunosuppressed. Also to prevent spread to his partners.
- Is he at risk for a disseminated infection? Answer: not at the moment
- Is this a potential STD? Answer: Yes.

Read the Fine Print

- CB is a 53 y/o AA homeless man with HIV, who was not in care.
- He presented with N+V, diarrhea, weight loss, anorexia, fever.
- He was found to have cryptococcal meningitis and disseminated MAC.
- His CD4 was 3 and VL 86276
- He was treated for his OIs and in preparation for HAART a genotype was sent.

His Genotype

hero V1.0701

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RESULTS

Protease:

RT:

INTERPRETATION (v.11 rules)

abacavir (ABC)	No Evidence of Resistance
didanosine (ddI)	No Evidence of Resistance
lamivudine (3TC)/emtricitabine (FTC)	No Evidence of Resistance
stavudine (d4T)	No Evidence of Resistance
tenofovir (TDF)	No Evidence of Resistance
zidovudine (AZT)	No Evidence of Resistance
delavirdine (DLV)	No Evidence of Resistance
efavirenz (EFV)	No Evidence of Resistance
nevirapine (NVP)	No Evidence of Resistance
amprenavir (APV)/fosamprenavir (FPV)	No Evidence of Resistance
APV/r or FPV/r	No Evidence of Resistance
atazanavir (ATV)	No Evidence of Resistance
ATV/r	No Evidence of Resistance
IDV/r	No Evidence of Resistance
indinavir (IDV)	No Evidence of Resistance
lopinavir + ritonavir (LPV/r)	No Evidence of Resistance
nefinavir (NFV)	No Evidence of Resistance
ritonavir (RTV)	No Evidence of Resistance
saquinavir (SQV)	No Evidence of Resistance
SQV/r	No Evidence of Resistance
tipranavir + ritonavir (TPV/r)	No Evidence of Resistance

But
there is
more

The fine print

- The astute HIV/ID consultant called the lab and requested the complete genotype which was already done, but not on the report.

Page 2, the fine print

VISIT ID: GMC
 DRAWN DATE: 05 07 07
 DATE OF REPORT: Thu May 29 2007 01:21 PM

Software: GeneObjecta 3.2 (2002/12/17 17:52:48 EST)
 Library: TRUGENE_HIV1_G11.gnl Thu Dec 15 2005 03:33 PM

Resistance mutations	Silent Mutations (at all positions)	Polymorphisms: coding changes not at resistant sites	Unexpected mutations at resistant sites
NONE	PR 91 (GTC) V11V (GAY) 88 (AAG) K20K (AAR) ** 198 (ATC) I86I (ATT) 282 (GGA) Q78Q (GGG) RT 214 (AGA) R72R (MGA) 228 (GAT) D76D (GAY) 288 (CCC) P87P (CCY) 295 (GGG) G99G (GGG) 298 (TTA) L100L (TTH) * 325 (CTG) L109L (YTA) 348 (TAT) Y115Y (TAY) * 421 (GGG) G141G (GGA) 424 (ATT) I142I (ATT) 454 (GAG) Q152Q (GGP) 514 (AGA) R172R (AGP) 544 (CAA) Q182Q (CAG) 595 (AGA) R198R (AGR) 610 (GAG) E204E (GAA) 643 (ACC) T215T (ACT) ** 655 (AAA) K219K (AAR) ** 664 (CAG) Q222Q (CAA) 676 (CCA) P226P (CCR) 697 (GAA) E233E (GAR)	PR 109 (AGT) S37N (AAT) RT 367 (GAC) D123E (GAA) 604 (ATA) I202V (TAA) 681 (AAG) R211K (AAA) 640 (CTT) L214F (TTT) 788 (GTG) V245M (ATG)	PR 187 (CTC) L83A (GCC)

Fine print enlarged

Polymorphisms:
coding changes not
at resistant sites

RTT
967 (GAC) D123E (GAA)
604 (ATA) L202I/V (rTA)
631 (AGG) R211K (AAA)
640 (CTT) L214F (TTT)
733 (GTG) V245M (ATG)

Given his Genotype, what ARV would you be most concerned about starting

- 20% A. 3TC
- 20% B. Abacavir
- 20% C. Nevirapine
- 20% D. Lopinavir/ritonavir
- 20% E. Don't know, would check online

Clinical Pearl

- Answer: you would be most concerned about the risk of an abacavir hypersensitivity reaction because of his V245M mutation.
- ABC hypersensitivity is strongly ass. With HLA B*5701 allele (100X risk)
- There is a very strong ass between the presence of HLA B*5701 and variations in the RT codon V245. CB has V245M
- Wild type V245 is strongly ass with not having the B*5701.
- Sensitivity and specificity for the presence of non-WT 245 predicting B*5701 is 96% and 75.5%.
- NPV is 99.6% (a WT 245 makes it safe to use ABC),
- PPV 20.4%,
- His HLA B*5701 test was sent and it was positive

CB Pearl

- Read the fine print
- The information is there at no additional charge, you may have to call.
- If no 245 variant, and the HIV is clade B it is safe to use ABC and no B*5701 test need be sent (cost saving).
- If it is positive, you may want to send a B*5701 test before using ABC.
- This mutant does not predict resistance.
- Great reference: Chui CK, Zabria LB, et al. A simple screening approach to reduce B*5701 associated ABC hypersensitivity on the basis of sequence variation in HIV RT. CID 2007;44:1503-8

PhenoSENSE GT™
COMBINATION HIV DRUG RESISTANCE ASSAY

Formerly VircoLogix, Inc.
Patrick Joseph, MD, Medical Director - 345 Oyster Point Blvd
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995 Potrero Avenue, Bldg 80, Ward 86
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San Francisco, CA 94110
USA

Client: 00126 Project: 00073
Phone: (415)626-2348 Fax: 4152068374

Date Collected: 10/03/2007 11:20 Date Received: 10/04/2007 21:15 Date Reported: 10/25/2007 12:08

Referring Physician: Daniel Wodarczyk Reference Lab ID

Gender: M Monogram Accession #: 07-143192
Mode: F,M,W Report Status: FINAL

HIV-1 Subtype:

DRUG	PHENOSENSE™ SUSCEPTIBILITY				Evidence of		Net Assessment	
	Generic Name	Brand Name	Cutoffs Lower - Upper	Fold Change	Increasing Drug Susceptibility	Decreasing Drug Susceptibility		Pheno Sensitive
NRTI	Abacavir	Zidovudine	(4.8 - 6.8)	1.26			Y	Y
	Didanosine	Videx	(1.3 - 2.2)	1.01			Y	Y
	Emtricitabine	Emtriva	(3.2)	1.16			Y	Y
	Lamivudine	EpiV	(3.6)	1.33			Y	Y Sensitive
	Stavudine	Zovir	(1.7)	1.35			Y	Y Sensitive
	Zidovudine	Retrovir	(1.5)	1.09			Y	Y Sensitive
NRTI Mutations				E44D				
NNRTI	Delavirdine	Rescriptor	(6.2)	1.49			Y	Y
	Etravirine	Sustiva	(3)	1.38			Y	Y
	Nevirapine	Vimavine	(4.5)	1.74			Y	Y
NNRTI Mutations				none				
PI	Atazanavir	Reyataz	(2.2)	0.57			Y	Y Sensitive
	Atazanavir	Reyataz / r ¹	(8.2)	0.57			Y	Y Sensitive
	Darunavir	Prezista / r ¹	(10 - 40)	0.84			Y	Y Sensitive
	Fosamprenavir	Lexiva	(2)	0.70			Y	Y Sensitive
	Fosamprenavir	Lexiva / r ¹	(4 - 11)	0.70			Y	Y Sensitive
	Indinavir	Crixivan	(2.1)	0.77			Y	Y Sensitive
	Indinavir	Crixivan / r ¹	(10)	0.77			Y	Y Sensitive
	Lopinavir	Kaletra	(9 - 85)	0.46			Y	Y Sensitive
	Nelfinavir	Viracept	(3.6)	1.12			Y	Y Sensitive
	Ritonavir	Norvir	(2.5)	0.90			Y	Y Sensitive
	Ritonavir	Invirase	(1.7)	0.88			Y	Y Sensitive
	Saquinavir	Intratec / r ¹	(2.3 - 12)	0.88			Y	Y Sensitive
Tazanavir	Aplisyn / r ¹	(2 - 8)	0.30			Y	Y Sensitive	
PI Mutations				I13V, L63P, V77V/I				

Lower Clinical Cutoff (in bold) Hyper-susceptibility Cutoff Sensitive Y Evidence of Drug Sensitivity
 Upper Clinical Cutoff (in bold) Biological Cutoff Partially Sensitive P Evidence of Partial Drug Sensitivity
 Resistant H Evidence of Drug Resistance

For more information on interpreting this report, please visit www.MonogramHIV.com or call Customer Service at 800-777-0177 between

Fine Print Exposed

Page 2 of Genotype shows all mutations detected.

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San Francisco, CA 94110
USA

Client: 00126 Project: 00073
Phone: (415)626-2348 Fax: 4152068374

Patient Name: [REDACTED] Date Collected: 10/03/2007 11:20 Monogram Acc#: 07-143192

Complete List of Mutations Detected

RT: K20R, E44D, A98A/S, Q102K, K122N/E, I155T, C162S, G196E, F214L, A272P, R277K, R284R/K, V292V/I, V293I, E297E/A
PR: T12A, I13V, L63P, I64V, V77V/I

This patient does not show the 245 mutation, and none of these mutations seem important as of 11/2007. As new drugs become available some of these mutations may indicate resistance to the new drugs. You need to archive these mutations for future reference.

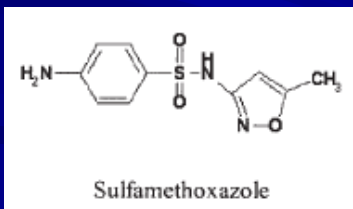
For example: 13 mutations that muted response to etravirine in the DUET trials-- V90I, A98G, L100I, K101E, K101P, V106I, V179D, V179F, Y181C, Y181I, Y181V, G190A, and G190S. .

To cross or not to cross

- RL is a man with AIDS, CD4 4, VL 80K, who has failed multiple regimens of HAART. His genotype and phenotypes show extensive 3 class failure. He declines injectable T-20
- His latest phenotypes shows that Darunavir (DRV) should have activity.
- He is able to get expanded access etravirine and raltegravir and he is given a Rx for DRV, ritonavir, and some nucs.
- When he picks up the meds the pharmacist tells him and gives him information sheets that say he should not take DRV because of sulfa allergy

DRV and Sulfa Cross Allergy

- In the past he had a rash and confusion with TMP-SMX, although there were confounding factors (speed use).
- What should you do? He has very limited options.



What should you do?

25% A. Avoid DRV, risk of allergy

25% B. Give DRV and monitor

25% C. Do a literature search

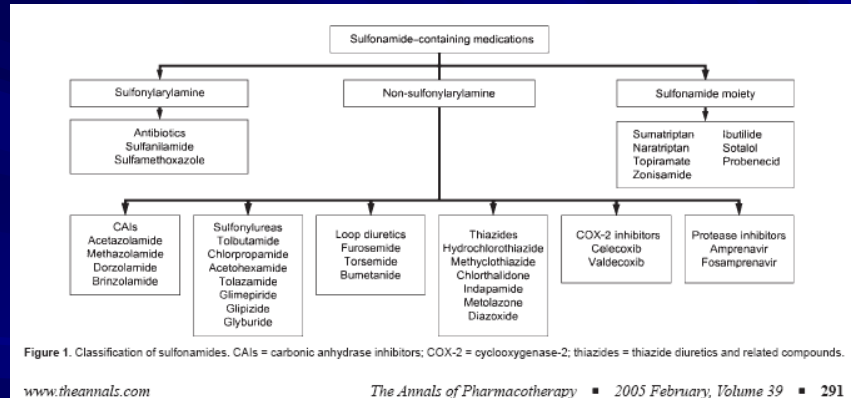
25% D. Consult a Pharm D.

Sulfonamide Cross Reactivity

- Sulfonamides can be divided into 3 groups
 - Sulfonamide moiety directly connected to benzene with an amine moiety at N4. (SMX, TMP-SMX (Septra, Bactrim))
 - Sulfonamide connected to benzene or cyclic structure without the amine at N4. (carbonic anhydrase Inh, sulfonyleureas, diuretics, PI amprenavir and Fosamp)
 - Sulfonamide not connected to benzene. (triptans, probenecid, sotalol)
- Retrospective UK cohort study: examined the risk of allergic reactions within 30 days of receiving a non-antibiotic sulfonamide.
 - Overall risk of allergic rxn to sulf antibiotic 4.8%
 - Risk of non-ab rxn after sulfa ab rxn 9.9%
 - Overall 2% allergic reaction after sulf non-antibiotic, 9.7% of those were severe.
 - If PCN allergic, not sulfa allergic, 14.6% had allergy to non-ab sulfa

Sulfonamide $-\text{SO}_2\text{NH}_2$, amine $-\text{NH}_2$, did you think organic chem would be useful?

Johnson KK, Green DL, et al. Sulfonamide cross reactivity: fact or fiction? *Annals of Pharmacotherapy* 2005;39:290-301



Sulfa Allergy

- The level of evidence is not good for most cases of antibiotic to non-antibiotic sulfonamide cross reactivity.
- Predisposition to allergic reaction to sulfas or other drugs (PCN) is a risk factor for allergic reaction.
- He came in early and took his meds and was observed for 3 hrs without problems, then insisted on leaving. His latest VL is < 75.
- It was safe to start darunavir given his history.

Sulfa References

- Strom BJ, Schinnar R, et al. Absence of cross reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. NEJM 2003;349:1628-35
- Johnson KK, Green DL, et al. Sulfonamide cross reactivity: fact or fiction? Annals of Pharmacotherapy 2005;39:290-301
- Our wonderful Pharm D. Ian McNichol.

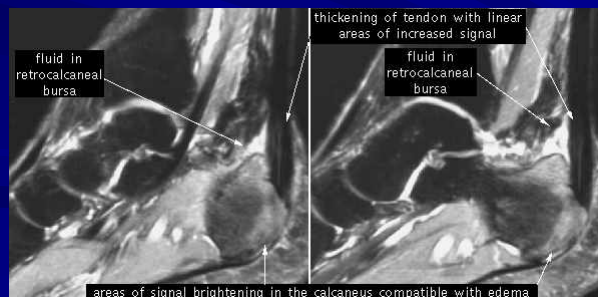
The Achilles Heel

- A 63 y/o man, CD4 219, VL <75, came to his scheduled appt. He had been seen on 5/23/2007 and treated for a urinary tract infection.
- He now complains of about 2 and ½ weeks of pain above his right heel. It hurts to walk. There has been no trauma.
- On exam pinching his right Achilles tendon causes him to shriek. His Achilles was irregular. His Thompson sign was negative (I will tell you how it is done later).

Not our Patient, but the Same Problem



- What important piece of history do you want to know?.
- A MRI was not done, but if it was done it might show the following.





■ Another MRI of another patient, NEJM 2007;357:2067 Images in clinical medicine.

Answer: you want to know what antibiotic he received.

- He had received levofloxacin for his UTI and his right Achilles began to hurt at the end of his 10 day treatment.
- Quinolone induced tendon rupture or tear is well described in the medical literature. It is not a common adverse effect. We should be warning our patients about it at the time of prescription.
- They should promptly stop it if they get pain in the Achilles, but it has also been described in the shoulder.
- Quinolones have a warning in their prescribing information in the package insert and PDR. Do not give it to pregnant women or children.
- Thompsons sign is absence of plantar flexion on squeezing the calf muscle in the prone position. It is positive in rupture or complete tear, but not in a partial tear.

Gold I, Igra H. Levofloxacin-induced tendon rupture: a case report and review of the literature. J Am Board Fam Pract 2003 16(5): 458-460

FQ Associated Tendon Rupture

- Mechanism: Studies have implicated ischemic, toxic, and matrix-degrading processes. Quinolone-induced tendon rupture more often occurs in less vascularized areas, which further supports an ischemic process. In an in vitro study, exposure of tendon tissue to ciprofloxacin showed a 60% to 68% decrease in fibroblast proliferation, a 36% to 48% decrease in collagen synthesis, a 14% to 60% decrease in proteoglycans synthesis, and a significant increase in matrix-degrading proteolytic activity after only 72 hours in culture.
- Risk factors for tendonitis/tendon rupture are concomitant steroid therapy and renal insufficiency] Other conditions include advanced age, prior tendonopathy, magnesium deficiency, hyperparathyroidism, diuretic use, peripheral vascular disease, rheumatoid arthritis, diabetes mellitus, and strenuous sports activities.
- Excess risk is calculated to be 3.2 cases per 1000 py years in those > 60 yrs old.
- Key Point: discuss the potential for tendon rupture with FQ, tell them what to look for and when to stop it and call. Don't give a FQ to pregnant women.

- Vyas H. Quinolone-associated rupture of the achilles tendon. NEJM 2007;357:2067 Images in clinical medicine.

Dizziness in Urgent Care

- 26 y/o Man came into urgent care complaining of dizziness. CD4 333, VL 6289, not on HAART. Started having a spinning sensation with nausea 2 days ago. Also some crying spells, trouble sleeping and some headaches, chills, but no fever,. No hearing loss or other neurological deficits.
- BP 120/70 pulse 78. He had his clonidine dose recently raised, he is on gabapentin, paroxetine (paxil), and quetiapine. He had been trying to get a hold of his psychiatrist for refills and has been out for 1 week. His exam was wnl.
- What do you think is going on?

SSRI Discontinuation Syndrome

Table 2. Percentage of DESS Reported by $\geq 10\%$ of Patients (in Descending Order by Pooled Treatments)

Symptom	Fluoxetine (n = 63)	Sertraline (n = 63)	Paroxetine (n = 59)
Worsened mood	22	28	45
Irritability	17	38	35
Agitation	16	37	31
Dizziness	3	29	50
Confusion	14	23	42
Headache	14	31	34
Nervousness	9	31	34
Crying	6	26	40
Fatigue	16	23	32
Emotional lability	13	31	26
Trouble sleeping	9	22	39
Dreaming	6	25	37
Anger	5	28	29
Nausea	6	14	40
Amnesia	8	17	24
Sweating	8	17	24
Depersonalization	8	17	21
Muscle aches	6	14	23
Unsteady gait	5	15	23
Panic	2	15	21
Sore eyes	6	14	15
Diarrhea	5	6	24
Shaking	2	11	21
Muscle tension	8	14	11
Chills	2	11	18

DESS, discontinuation-emergent signs and symptoms.

← Paroxetine

← Dizziness
50%

← Nausea
40%

SSRI Discontinuation Syndrome

- Our patient has pretty classic findings. Paroxetine (paxil) is among the most frequent causes, as it has a short half life compared to fluoxetine (prozac).
- His symptoms resolved after 1 day of being back on his medications. At times the symptoms can be more dramatic and consist of paresthesias and headaches which can lead to ER visits as the patient may feel they are having a stroke.
- Pearl: Patients need to be reminded about these symptoms and not to run out. Current pharmacy plans may be a problem.

- Reference: Rosenbaum JF, Fava M. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized controlled trial. *Biol Psychiatry* 1998;44:77-87.

Med Refill

- A patient of mine came in for a refill of his opiates that he uses for chronic pain. He also asked for Viagra.
- A diagnostic test was performed

Daneill HW. Hypogonadism in men consuming sustained action oral opiates. J of Pain 2002;3:377-384

Table 2. Average Hormone Levels in Men Consuming Sustained-Action Opioids in Multiple Daily Doses

METHADONE EQUIVALENTS (DAILY CONSUMPTION)	No. OF MEN	AGE AVERAGE (YEARS)	TESTOSTERONE					FSH (mIU/mL)	ESTRADIOL (pg/mL)†
			FREE (pg/mL)	TOTAL* (ng/dL)	DHT (ng/dL)	LH (mIU/mL)			
0	27	57.4	127.4 (±48.8)	449.1 (±181.1)	39.3 (±22.3)	6.1 (±3.5)	8.8 (±8.5)	32.0 (±17.2)	
20-60 mg	15	51.9	74.3 (±43.5)	265.8 (±191.9)	20.4 (±11.6)	4.6 (±2.5)	8.1 (±7.5)	18.7 (±8.4)	
70-120 mg	23	49.4	41.7 (±25.5)	188.5 (±193.4)	17.6 (±16.7)	4.6 (±3.1)	4.7 (±4.3)	14.7 (±8.9)	
>120 mg	16	47.8	44.8 (±26.3)	172.1 (±108.8)	15.0 (±9.7)	2.4 (±1.3)	4.3 (±2.4)	11.7 (±6.3)	
Normal range			50-210	260-1000	25-75	2-18	1.6-18.1	21-50	

Abbreviations: DHT, dihydrotestosterone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

NOTE. Figures in parenthesis indicate standard deviation of each mean.

*Conversion factor to nmol/L = 0.0347.

†Conversion factor to pmol/L = 3.671.

- A serum testosterone level was sent

A Testosterone Level was sent

- Chronic opiates can have profound effects on gonadal hormones. Specifically opiates, and this is well described with methadone, suppress the gonadal axis. Levels of the hypothalamic releasing hormones and testosterone synthesis may greatly decrease. Higher doses are worse. Erectile problems do not always correlate well with testosterone levels.
- My patient's testosterone level was 40, the lowest I had ever seen. I will send other tests to confirm whether it is primary or secondary. The head of the UCSF pain clinic, noted that she sees this problem often and has had men with undetectable testosterone levels.
- Women may have suppression of their hypogonadal axis and become amenorrheic or have menstrual abnormalities on chronic opiates.
- Hypogonadal men and women are at increased risk of osteoporosis.

How do you spell relief?

- A pt of mine who has just started salvage therapy including raltegravir, etravirine, darunavir, ritonavir, and tenofovir, FTC.
- He gets GERD and being conscientious, he asks what he can take for it.
- You know that atazanavir and acid suppression don't mix, but he is not on it.
- What do you advise.

Antacid Therapy, which one to avoid?

25% A. Proton pump inhibitors

25% B. Calcium containing

25% C. H2 blockers

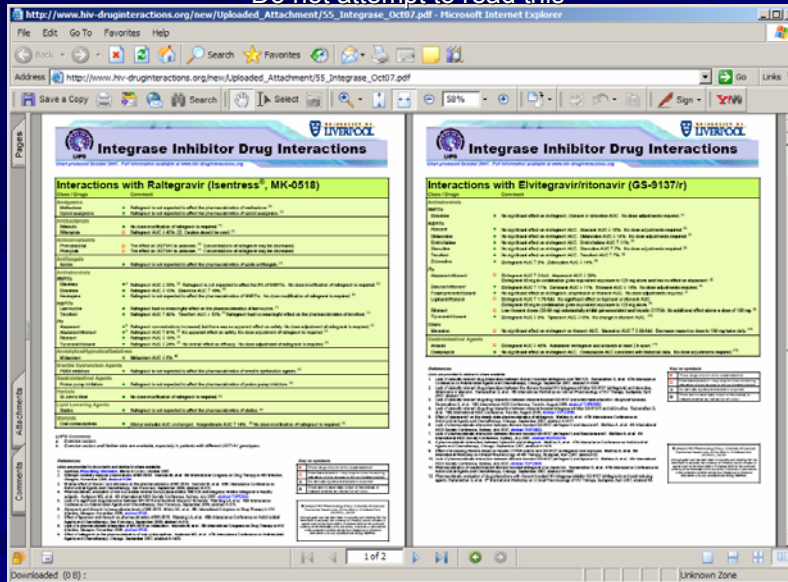
25% D. All are ok to take

Avoid Divalent Cations, like Calcium Carbonate

- Pharmacokinetic studies with elvitegravir and antacids (which contain divalent cations) have been shown to reduce elvitegravir levels (AUC by 45%, C_{max} 47%, C_{min} 41%) (Ramanathan S, et al. Poster #69, 8th IWCPHT). This is NOT due to the acid lowering effect, but rather to the cations present in the antacid compounds. Omeprazole did not lower levels nor did antacid given > 4 hours after Elvitegravir.
- Until data becomes available on raltegravir and antacids (TUMS, Maalox, Mylanta, Rolaids, Pepto-Bismol, etc) or other polyvalent cations (e.g., calcium, iron, multivitamins, nutritional supplements), concomitant administration of raltegravir and antacids/divalent cations should be used with caution.
- Bonus, he also takes a selenium supplement for his diabetes, what should you do?

Information from Ian McNichol, Pharm D PHP SFGH

Do not attempt to read this



Not intended to be read, but this website from the University of Liverpool has drug interaction sheets and much more information. It has the antacid information.

www.hiv-druginteractions.org also check <http://hivinsite.ucsf.edu/> drug interactions data base

Detail from the Elvitegravir Chart

Ritonavir	<ul style="list-style-type: none"> ❑ Low ritonavir doses (20-50 mg) substantially inhibit gut-associated and hepatic CYP3A. No additional effect above a dose of 100 mg. [9] ◆ Elvitegravir AUC ↓ 8%. Tiplranavir AUC ↓ 10%. No change in ritonavir AUC. [10]
Tiplranavir/ritonavir	
Others	
Maraviroc	<ul style="list-style-type: none"> ❑ No significant effect on elvitegravir or ritonavir AUC. Maraviroc AUC ↑ 2.86-fold. Decrease maraviroc dose to 150 mg twice daily. [11]
Gastrointestinal Agents	
Antacid	<ul style="list-style-type: none"> ❑ Elvitegravir AUC ↓ 45%. Administer elvitegravir and antacids at least 2 h apart. [12]
Omeprazole	<ul style="list-style-type: none"> ◆ No significant effect on elvitegravir AUC. Omeprazole AUC consistent with historical data. No dose adjustments required. [12]
References	
<p>Links are provided to abstracts where available</p> <ol style="list-style-type: none"> Lack of clinically relevant drug interactions between ritonavir-boosted elvitegravir and TMC125. Ramanathan S, et al. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, September 2007, abstract H-1040. Lack of clinically relevant drug interactions between the ritonavir boosted HIV integrase inhibitor GS-9137 (elvitegravir) and stavudine, didanosine or abacavir. Ramanathan S, et al. 8th International Workshop on Clinical Pharmacology of HIV Therapy, Budapest, April 2007, abstract 70. Lack of clinically relevant drug-drug interaction between ritonavir-boosted GS-9137 and emtricitabine/tenofovir disoproxil fumarate. Ramanathan S, et al. 16th International AIDS Conference, Toronto, August 2008, abstract TUPE080. 	
<p>Key to symbols</p> <ul style="list-style-type: none"> ● These drugs should not be coadministered ❑ Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration ◆ No clinically significant interaction expected ○ There are no clear data, actual or theoretical, to indicate whether an interaction will occur 	

- Peril: on new HIV medications know where to look up potential drug interactions and check before prescribing.

University of Liverpool www.hiv-druginteractions.org

The CD8 Count, is it Worth the Money

- An experienced HIV provider noted that some study labs and labs from other providers had not only CD4, CD4%, and VL, but CD8 and CD4/CD8 ratio.
- She asked, “should I be sending these on my patients?”

The CD8 provides useful clinical information beyond the CD4 and %

33% A. True

33% B. False

33% C. Don't know, but better to send

Lots of Labs, what do they mean?

IMMUNOLOGY, CELLULAR (Up to 99 latest results)

	2007 05 Nov 12:45	2007 05 Nov 11:55	2007 07 Jul 10:30	2007 07 Mar 09:45	2007 07 Jan 17:45	2006 06 Oct 14:50	2006 06 Jul 09:05	2006 06 May 10:25	2006 06 May 08:40	2006 06 Jan 15:10	2005 05 Oct 09:50	2005 05 Jul 09:40	2005 05 May 09:30	2005 05 Apr 09:15
<input type="checkbox"/> %CD4 (28-59) %	20 L		17 L	15 L	16 L	16 L	13 L	16 L		16 L	15 L	13 L	12 L	14 L
<input type="checkbox"/> %CD8 (17-46) %			48 H	49 H				49 H		51 H	49 H		51 H	
<input type="checkbox"/> %CD4 (28-59) %														
<input type="checkbox"/> Absol CD4 T Cell (420-1250) cells/uL	311 L		318 L	224 L	325 L	245 L	220 L	244 L		238 L	199 L	196 L	169 L	182 L
<input type="checkbox"/> Absol CD8 T Cell (220-960) cells/uL			881	721				776		767	662		700	
<input type="checkbox"/> Comments														
<input type="checkbox"/> Help/Sup Ratio (0.60-3.20)			0.35 L	0.31 L				0.33 L		0.31 L	0.31 L		0.24 L	
<input type="checkbox"/> HIV VIRAL LOAD														

This patient's VL have been < 75 on HAART for years.

CD8

- Progressive HIV infection is characterized by
 - Decline in CD4 count
 - Increase in CD8 count, initially, followed later by a decline
 - Inversion of the CD4/CD8 ratio to < 1.0.
- Normal CD4/CD8 ratio is between 1-3.2 and may be determined genetically
- Decline in the ratio to < 1.0 has prognostic information about progression and likelihood of Long term nonprogression (CD4 > 500 for 10 years without HAART), rates of 9-11%.
- What is the clinical relevance in the HAART era?
- Cost at SFGH Lab: CD4 and % \$129, CD4 and CD8 \$257, reagent cost is the same as CD4 only. At SFGH > 50% of CD4 counts are ordered with CD8*

*personal communication with SFGH Lab 11/15/2007

If > 2 years before CD4/CD8 inversion (ratio < 1.0) lower rates of progression to AIDS

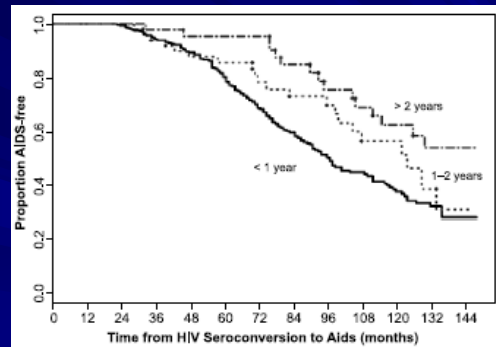


FIGURE 2. Kaplan-Meier survival curves for AIDS-free survival according to the length of time from HIV-1 seroconversion to inversion of the CD4/CD8 ratio. To obtain an unbiased analysis, men who developed AIDS within 2 years of seroconversion ($n = 7$) were excluded from this analysis. Therefore, there are no events in the first 24 months. The curves were highly statistically different ($P = 0.0003$).

Margolick JB, Gange SJ. JAIDS;42:620-626. MACS cohort study, pre-HAART era

Preserved CD4/CD8 > 1.0 at 2 years post seroconversion is associated with long-term nonprogressors

J Acquir Immune Defic Syndr • Volume 42, Number 5, August 15, 2006 *Impact of Inversion of the CD4/CD8 Ratio*

TABLE 4. Characteristics of Long-Term Nonprogressors

Participant No.	Year of Seroconversion	Time to Inversion of CD4/CD8 Ratio (mo)	CD4 Cell Count 10 Years After Seroconversion (cells/ μ L)	Data 2 Years After Seroconversion	
				Viral Load	CD4/CD8 Ratio
1	1986	110	691	893*	1.90
2	1985	56	724	8900*	1.75
3	1984	142	738	<400	1.64
4	1988	110	774	551	1.48
5	1984	3	883	21,830	0.86
6	1984	142	949	<400	1.37

*Calculated as the mean of 2 visits 2 to 3 months before and after this time.

5 of the 6 LTNG maintained their ratio > 1

- Pearl: I am not sure what the clinical utility of the CD8 or CD4/CD8 ratio once the ratio has become < 1. If the result will not effect management why send it?

A tough pill to swallow

- 51 y/o W with AIDS, CD4 77, VL >500K , not on HAART.
- Presented with hematemesis, odynophagia, dysphagia, anorexia weight loss, abdominal pain and fever.
- Admitted and had an EGD that showed an esophageal ulcer and hemorrhagic gastritis. She was put on pantoprazole and fluconazole and discharged only to be readmitted with the same problems and dehydration.

Tough Pill

- In the interval between hospitalizations she was unable to start HAART
- Review of her pathology showed that her esophageal ulcer had CMV inclusion bodies.
- IV ganciclovir was started and she had some improvement and she was switched to po valganciclovir.
- As an outpatient lopinavir/r, FTC and tenofovir were started. Her CBC was monitored.
- An ophthalmology consultation did not show any CMV retinitis.

CMV Esophagitis



Medscape®

<http://www.medscape.com>

Recommended Duration of anti-CMV therapy?

- 25% A. Until the CD4 is > 100 for 6 months
- 25% B. Until her CD4 is > 200
- 25% C. 3-6 weeks at induction dosage then stop
- 25% D. 14-21 days induction then maintenance therapy

CMV GI Disease and HIV Pearls

- Occurred in up to 5% in pre-HARRT era, CD4 usually < 50, median 15-21. Reactivation of latent disease.
- Pre-HARRT era associated with high AIDS rel. mortality, median survival 7.6-10 mos. Relapse rate variable, 20% at Grady Hosp.
- Most common GI sites esophagus (multiple distal) and colon.
- Ass. with CMV retinitis. New extracolonic CMV disease developed in 7 (23%) of 30 placebo patients and in 3 (9%) of 32 ganciclovir patients in only 14 days (P = .026).
- Diagnostic triad: clinical symptoms, endoscopic visualization of ulcers or erosions, pathologic CMV inclusion bodies. CMV Ab or viremia not diagnostic.

GI CMV Disease

- Treatment: induction therapy for 3-6 weeks with IV ganciclovir 5mg/kg BID (grade 1B) or foscarnet 90 mg/kg BID (grade 2B). Switch to po induction doses of Valganciclovir 900 mg BID when symptoms are improved.
- Optimal duration is unclear, consensus panel recommends 3-6 weeks (grade 1B). Inclusion bodies may clear in 3 weeks, ulcer healing in 6 in one series.
- Maintenance therapy for those who have relapsed, re-induce then valganciclovir 900 mg/day
- HAART is an essential part of Rx. HAART era dramatic decreases in CMV end organ disease and mortality. EuroSida pre-HAART 6.2/100 pt yrs vs HAART 0.3
- Need to exclude CMV retinal disease as treatment is different.

CMV GI References

- Jacobson MA. AIDS related cytomegalovirus gastrointestinal disease. Chapter in Uptodate, last revised 2/1/2007
- Wilcox CM, Schwartz DA. Esophageal ulceration in HIV infection: causes, response to therapy and long-term outcome. *Ann Intern Med* 1995;123:143-149.
- Yust I, Fox Z. Retinal and extraocular cytomegalovirus end-organ disease in HIV pts in Europe: a EuroSIDA, 1994-2001. *Eur J Microbiol Infect Dis* 2004;23:550-559.
- Guidelines for the treatment of CMV diseases with AIDS in the era of potent ARV. Recommendations of an international panel. (includes Mark Jacobson) *Arch Intern Med* 1998;158:957-969
- Dieterich DT. Multiple references including. *J Infect Dis*. 1993 Feb;167(2):278-82. Ganciclovir treatment of cytomegalovirus colitis in AIDS: a randomized, double-blind, placebo-controlled multicenter study.

P.S. the patient is doing well, gaining wt and is free of eye disease. Her Valganciclovir has been stopped and she continues on HAART.

Facial Swelling

- 51 y/o W with AIDS and HTN.
- She is on HAART containing lopinavir/ritonavir, tenofovir and FTC.
- She has HTN and was put on amlodipine to help control her BP.
- After being on both these meds she develops facial swelling.
- What do you think is going on?

Facial Swelling

- Amlodipine edema has been reported, usually in the lower extremities, but also in the upper extremities and facial edema.
- Amlodipine levels can be increased by potent CYP3A4 inhibitors like the lopinavir/ritonavir that she is on.
- **Drug Interactions Substrate** of CYP3A4 (major); **Inhibits** CYP1A2 (moderate), 2A6 (weak), 2B6 (weak), 2C8 (weak), 2C9 (weak), 2D6 (weak), 3A4 (weak)
- CYP3A4 inhibitors: May increase the levels/effects of amlodipine. Example inhibitors include azole antifungals, clarithromycin, diclofenac, doxycycline, erythromycin, imatinib, isoniazid, nefazodone, nifedipine, propofol, protease inhibitors, quinidine, telithromycin, and verapamil.
- Grapefruit juice: May modestly increase amlodipine levels.
- Clinical Peril: Protease inhibitors can increase the levels of calcium channel blocker antihypertensives and increase the adverse effects, like the edema from amlodipine. You need to look up possible drug interactions.

[Ganeshalingham A, Wong W.](#) Amlodipine-induced bilateral upper extremity edema
Ann Pharmacother. 2007 Sep;41(9):1536-8. Epub 2007 Jul 31. Links

Amlodipine Facial Edema

The mechanism of amlodipine-related edema is unclear. It is thought to be a direct effect of the drug on local vasculature.^{2,8} The resulting uncompensated arteriolar vasodilatation increases intracapillary hydrostatic pressure, thereby exuding fluid into the interstitium.^{6,8} Because calcium-channel antagonists have a natriuretic effect, salt retention or fluid overload has not been reported as the main mechanism.⁸ In our patient, the onset of edema occurred 19 days after amlodipine was started. Complete resolution occurred 3 days after discontinuation of the drug and was associated with a 1.2 kg weight loss. It is likely that several underlying mechanisms are involved in edema formation.

[Ganeshalingham A, Wong W.](#) Amlodipine induced bilateral upper extremity edema. Ann Pharmacother 2007;41: 1536-8

Messerli FH, Oparil S, Feng Z. Comparison of efficacy and side effects of combination therapy of angiotensin-converting enzyme inhibitor (benazepril) with calcium antagonist (either nifedipine or amlodipine) versus high-dose calcium antagonist monotherapy for systemic hypertension. *Am J Cardiol.* 2000 Dec 1;86(11):1182-7.

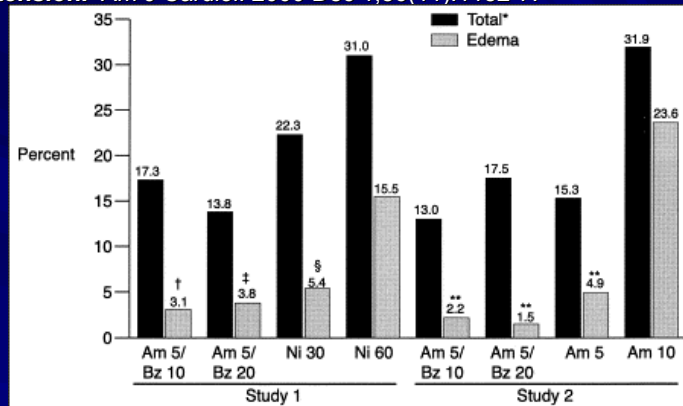


Figure 2. Frequency of total adverse events and edema in studies 1 and 2. *Occurring in $\geq 2\%$ of patients; † $p < 0.001$ compared with Ni 60 mg; ‡ $p \leq 0.001$ compared with Ni 60 mg; § $p = 0.008$ compared with Ni 60 mg; ** $p < 0.001$ compared with Am 10 mg. Abbreviations as in [Figure 1](#).

Asleep in Social Work

- I was called to see a woman, Ms.K. who was very difficult to arouse in the social work office
- 40 y/o W, not on HAART, CD4 313
- VS AF, 126/76, 78,pulse Ox 97%. Looked comfortable, asleep in a chair
- Difficult to arouse, quickly fell back asleep
- SW says she is often like this, but when she first walked in she was alert, answered questions.

Sleepless in the TL

- She is homeless, stays in the Tenderloin (TL). Uses crack.
- She is up at night walking around
- Has a diagnosis of depression and is on paroxetine. TSH and T4 were wnl 1 year ago.
- She says that when she was in jail they had to wake her up for meals.
- What is your differential diagnosis for her excessive sleepiness?

DDX of Excessive Daytime Sleepiness

- Excessive daytime sleepiness is reported by up to 31% of the adult population.
- Consequences include: accidents; impaired work and school performance,; and psychosocial functioning.
- In most cases an etiology can be found.
- Most common cause is chronic sleep deprivation. Sufficient sleep = person awakes rested and restored rather than a specific # of hrs. It is cumulative. Shift workers, med. house staff.

DDX of Excessive Daytime Sleepiness-OSA

- Obstructive sleep apnea. In gen. pop. 2% of women, 4% of men
- More common in adults, men, snorers, post-menopausal women, elderly, and obesity. 1/3 are not obese.
- Excessive sleepiness is caused by sleep fragmentation. Leads to HTN, R heart failure, pulmonary HTN, polycythemia, HAs
- Need formal sleep study to accurately Dx and titrate CPAP treatment.

DDX of Excessive Daytime Sleepiness-Narcolepsy

- As common as Parkinson's Dis. 0.09%, 250,000 in US.
- Genetic component 90% are HLA-DR2/DQ1, but found in 30% of gen. pop.
- Onset adolescence and early adult.
- Clinical signs, less than half have all the signs.
 - Excessive daytime sleepiness, sleep attacks
 - Cataplexy sudden loss of muscle tone, typically triggered by emotion. (65-70%)
 - Hypnagogic (at sleep onset) and hypopompic (upon awakening) hallucinations, vivid frightening(12-50%)
 - Sleep paralysis (60%)
 - Automatism, awake, but not fully aware (80%)
 - Pathophys impaired control of boundaries between wakefulness and REM and non-REM sleep
 - Need objective sleep studies, polysomnography and multiple sleep latency testing (MSLT)

Mahowald M. What is causing excessive daytime sleepiness. Postgraduate medicine 2000;107:108-23. And Uptodate.com

DDX of Excessive Daytime Sleepiness-Medication or Withdrawal

- Sedative-hypnotics barbs, benzos, and newer sleeping pills. Methadone “nodding”, especially when combined with clonazepam and other sedatives.
- Cocaine withdrawal: When cocaine use is stopped or when a binge ends, a “crash” follows almost immediately. This crash accompanied by a strong craving for more cocaine. Additional symptoms include fatigue, lack of pleasure, increased appetite, depressed mood, anxiety, irritability, sleepiness, slowing of activities, vivid and unpleasant dreams, and sometimes agitation or extreme suspicion. After initial sleepiness, insomnia can continue.

<http://www.nlm.nih.gov/medlineplus>

Further Hx and My Dx

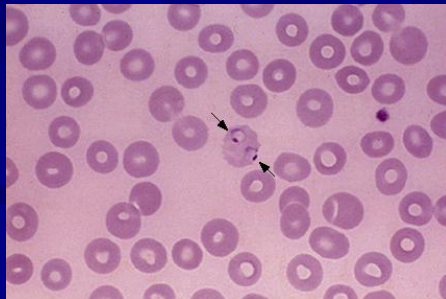
- I did a complete sleep history
- She spends her nights in the TL, is homeless, walks the street, some commercial sex work and frequent crack cocaine use. She is fearful to sleep in the TL. Does not use any opiates or other sedatives.
- Telephone call to the jail HIV doctor reveals that she was not excessively sleepy while incarcerated.
- My working diagnosis is multifactorial excess sleepiness due to chronic sleep deprivation, night time stimulant use (crack cocaine), reversal of day-night sleep cycle, fear of sleeping in unsafe areas at night.

Sleepy

- She was accompanied by 2 of our staff to her shelter plus interview, after coffee, they sat on each side of her prodding her to stay awake.
- Plan: work toward obtaining safe housing, drug treatment, psychiatric evaluation, continuing her primary care. Urine tox shows only the presence of cocaine.
- I saw her last week and she was totally alert and stayed awake and had housing leads and felt less depressed.
- Pearl: consider a broad Ddx of excessive sleepiness and include psychosocial factors. Housing may be the definitive treatment.

A Clinical Question

- A colleague asks, “what are the interactions of HIV and Malaria given that the 2 diseases have a huge overlap in sub-saharan Africa”?



Malaria and HIV: Which are True

20% A. CD4 <200 is a risk for malaria

20% B. HIV increases risk of placental malaria

20% C. Malaria increases VL & decreases CD4

20% D. TMP/SMX reduces malaria by 70%

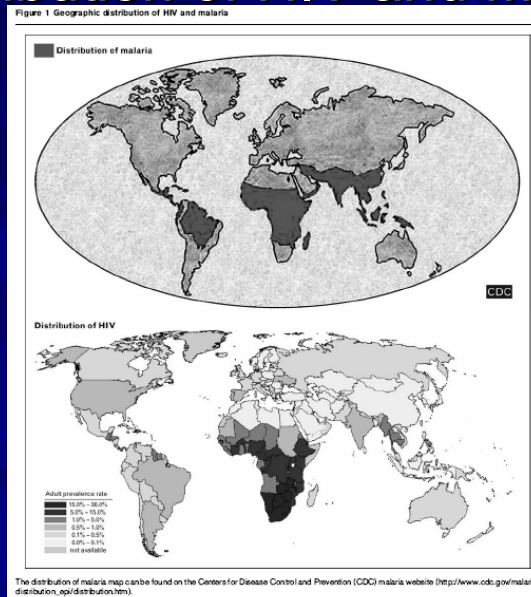
20% E. All are true

Distribution of HIV and Malaria

Malaria

HIV

Darker indicates higher rates



From the CDC and Slutsker L. HIV and malaria: interactions and implications. Current Opinion in Infectious Disease 2007;20:3-10

Malaria and HIV

- *P. falciparum* causes severe disease and death largely in people lacking specific acquired immunity.
- Immunity develops in the face of high rates of transmission. Adults in those areas tend to be parasitemic, but asymptomatic. Suggest HIV testing in adults who present with clinical malaria in a region where natural immunity normally develops.
- In areas without stable transmission, HIV is a risk factor for severe malaria in young children and adults
- In areas with high transmission, HIV only modestly increases the risk of parasitemia and clinical malaria.

Malaria and HIV

- Risk of malaria is increased with decreasing CD4, but less associated with HIV immunosuppression than other OIs. Uganda clinical malaria OR 6.1 for CD4 <200 compared to >500. Increased severity in areas of unstable malaria transmission.
- Acquired immunity helps in the clearance of drug resistant parasites. HIV has been shown to impair acquired immunity and the response to therapy.
- HIV may be associated with increased re-infection due to weakened immune response to liver stage parasites.
- Malaria infection increases viral load transiently (up to 8 wks) and lowers CD4 about 40 cells, successful therapy increases CD4
- Anopheles mosquitoes are more likely to bite febrile hosts.

Malaria and HIV

- In Uganda, CTX(TMP-SMX) prophylaxis in pts with CD4 <500 showed a 70% reduction in febrile malaria.
- ART prevented an addition 50% of malaria associated fevers.
- Insecticide treated bed nets also further decreased risk
- Although there are large number of potential drug interactions and overlapping toxicity little is known about interactions between malaria medicines and ART
- CTX may be ass. With higher rates of sulfadoxine-pyrimethamine (Fansidar) treatment failure in children

Drug Interaction

- A study to evaluate potential interactions between the combination of amodiaquine plus artesunate (AQ/AS) and the HIV non-nucleoside reverse transcriptase inhibitor, efavirenz. The study was prematurely discontinued after the first two patients developed severe asymptomatic hepatotoxicity more than one month after study completion. No other etiology for the marked flare in aminotransferases was identified. The addition of efavirenz resulted in significant increases of amodiaquine serum concentrations in both patients (AUC increased by 115 and 302 percent, respectively).
- Aminotransferases should be monitored in patients taking regimens that include these medications.

German, P, Greenhouse, B, Coates, C, et al. Hepatotoxicity due to a drug interaction between amodiaquine plus artesunate and efavirenz. Clin Infect Dis 2007; 44:889.

Selected Drug Interactions

Table 4. Selected Drug Interactions Involving Antimalarials and ARVs or Other Selected Medications Commonly Used in the Care of HIV-Infected Patients in Sub-Saharan Africa

Antimalarial	ARVs and Other Medications ^a	Drug-Drug Interactions ^b
Amodiaquine	Efavirenz, saquinavir, lopinavir, tipranavir	Decreased metabolism of amodiaquine as a result of inhibition of CYP2C8; likely increased risk of amodiaquine-related hepatic and hematologic toxicity ^{1,2,3} ; hepatotoxicity has been observed in healthy volunteers given efavirenz and amodiaquine ¹
Artemisinin	Ketoconazole	Antagonism observed in vitro; clinical significance unknown ⁴
Atovaquone	Atazanavir sulfate Lopinavir Rifampin Ritonavir, tipranavir	Combination may decrease level of atovaquone; clinical significance unknown ^{5,6}
Atovaquone	Zidovudine	Decreases oral clearance of zidovudine; clinical significance unknown ⁷
Dapsone	Rifampin	Decreases level of dapsone ⁸
Dapsone	Stavudine	May increase risk of peripheral neuropathy ⁹
Dapsone	Co-trimoxazole ^c	May increase level of dapsone ¹⁰
Doxycycline hydrochloride	Rifampin	May decrease level of doxycycline ¹¹
Halofantrine hydrochloride	PIs, NNRTIs	ARV effects on cytochrome P450 3A4 metabolism may cause inhibition of halofantrine metabolism with risk of significant cardiotoxicity ¹²
Lumefantrine	PIs, NNRTIs	Controversial; theoretically, combination may cause Q-T interval prolongation; manufacturers recommend against combining; others, including WHO, refute recommendation as not supported by evidence ^{13,14,15,16}
Proguanil hydrochloride	Ritonavir	Ritonavir may inhibit conversion of proguanil to cycloguanil; clinical significance unknown ¹⁷
Quinine	Ritonavir, delamanid mesylate, ritonavir-boosted PI regimens	Quinine levels may be increased by ARV-provoked inhibition of cytochrome P450 3A4 activity; risk of cardiac toxicity (Q-T interval prolongation) ¹⁸
Quinine	Nevirapine, efavirenz	ARV-related induction of CYP-3A4 activity may decrease levels of quinine to subtherapeutic range ¹⁹
Quinine	Rifampin	Increased clearance of quinine resulting in 5-fold increase in likelihood of malaria recrudescence after treatment ²⁰
Sulfadoxine-pyrimethamine	Co-trimoxazole Zidovudine	Combination may further increase risk of bone marrow toxicity ²¹
Sulfadoxine-pyrimethamine	Co-trimoxazole	Known malaria cross-resistance between pyrimethamine and trimethoprim ²²

^a Abbreviations: ARVs, antiretrovirals; HIV, human immunodeficiency virus; NNRTIs, nonnucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; WHO, World Health Organization.
^b Antiretrovirals and selected other medications commonly used in HIV-infected patients in sub-Saharan Africa.
^c Selected drug-drug interactions that may result from concurrent therapy (not a complete list).
^d A combination of trimethoprim and sulfamethoxazole.

Brentlinger PE, Behrens CB, Kublin JG. Challenges in the prevention, diagnosis, and treatment of malaria in HIV infected adults in Sub-Saharan Africa. Arch Int Med 2007;167:1827-36

Malaria and HIV

- Benefits of parity are decreased with HIV.
- HIV is associated with increased peripheral and placental parasites.
- Co-infection increases rates of: low birth weight, more preterm, maternal anemia, intrauterine growth retardation. Post natal mortality.
- Question of increased MTCT?

Shared Signs and Symptoms

- Malaria and HIV ass. OIs and other infections and IRIS share a broad range of symptoms and signs. Clinicians need to consider malaria as well as other infections. Over-treatment may speed resistance.
- Fever, most widely recognized manifestation of malaria, but all fevers should not be ascribed to malaria
- Anemia, 10% of co-infected pts have a HB <7 on hosp admission.
- Respiratory syndromes, 3-10% of pts with P.falc have pulm symptoms. Cough can occ in up to 50%. Pulmonary edema can be a fatal manifestation.
- GI and hepatobiliary symptoms of nausea, vomiting, hepatosplenomegaly, jaundice, abd pain, and elevation of liver enzymes have been reported in acute malaria.
- Neurologic symptoms of HA, mental status changes, coma, and seizures can occ in acute malaria. Cerebral malaria is treated with quinine, NNRTIs and rifampin can decrease quinine levels, Boosted PIs can increase quinine levels and toxicity.
- Lactic acidosis can occur in severe malaria.

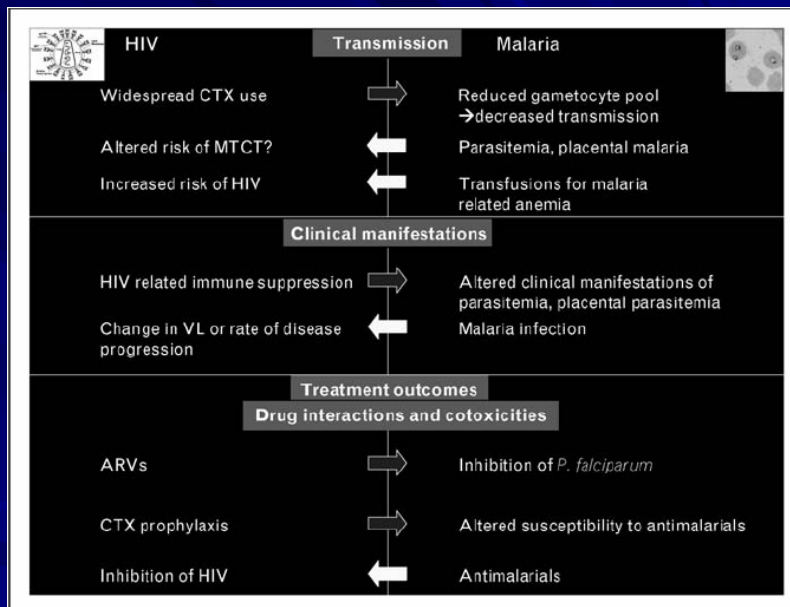
Brentlinger PE, Behrens CB, Kublin JG. Challenges in the prevention, doagnosis, and treatment of malaria in HIV infected adults in Sub-Saharan Africa. Arch Int Med 2007;167:1827-36

Malaria and HIV

- Effects of Malaria on HIV
- Increased HIV viral load in blood and placenta. VL increases usually transient.
- May accelerate HIV course if chronic or untreated.
- May increase sexual transmission due to higher VL, definitive studies lacking.
- Severe anemia may require blood transfusion and may lead to infection and limit AZT use

Summary of Malaria and HIV

- HIV is a risk for severe malaria in areas without high transmission.
- Risk of malaria increases with low CD4, but less effect than other OIs
- Co-infected pts respond poorer to therapy
- Increased rates of malaria re-infection in HIV.
- CTX decreases malaria infection
- Loss of protection from parity in HIV+ women
- Higher rates of fetal complications
- Malaria increases HIV VL, usually transiently
- Increased sexual transmission, ? MTCT
- Anemia limits AZT use



Brentlinger PE, Behrens CB, Kublin JG. Challenges in the prevention, doagnosis, and treatment of malaria in HIV infected adults in Sub-Saharan Africa. Arch Int Med 2007;167:1827-36

Why Won't He Take His Meds?

- A 52 y/o homeless man presented to the hospital for worsening SOB, one of many hospitalizations for this problem
- Thin, CD4 3 , VL 84K, Dx with HIV in 2001, never on HAART
- Other problems included CHF stage 4, global hypokinesia and ankle osteomyelitis, and episodic crack use, past PCP.
- Our staff was able to get him into permanent housing in a newly remodelled apt. building. It was the first place of his own that he had. He wanted his sister to see it and be the first to sleep on the bed so he slept on the floor.

No Meds

- We had a great relationship with him, we had gotten him housing and benefits. He enjoyed coming to the clinic and liked his PCP.
- His health worsened and he was able to get to Maitri. It was the nicest place he ever stayed in. He had a few hospitalizations for CHF, usually leaving AMA because he felt better or did not like the food or needed to do something. Would never take a lumbar puncture
- Our clinic outreach worker, Lee, paid for his daughter to come out and visit him.
- He died peacefully at Maitri surrounded by people who cared about him.
- Why was he unable to take meds?

DDx of Not Taking Meds

- Cost of meds, not a factor here, he had Medicaid
- Adverse side effects, he never tried the meds, but was fearful of the HIV meds turning him darker.
- Chaotic life style, he had medisets delivered and later was in a place with onsite nursing, he still could not do it.
- Substance use, yes he had that problem, but he was a very functional person, always polite
- Psychiatric, no apparent psychosis

The Main Reason

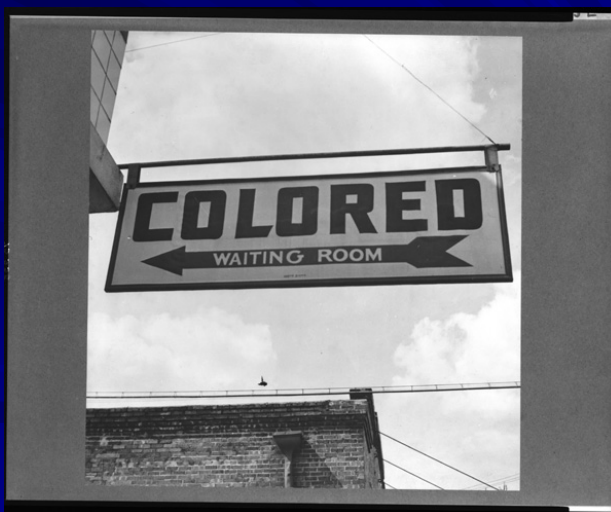
- The reasons for him not taking meds are likely to be complex and multifactorial
- We found out that his father was experimented on in the Tuskegee study*. Our patient was born with syphilis.
- He grew up down south in Alabama and was 53 y/o (which should have been a red flag). He grew up in the times of strict segregation and discrimination. He was not able to read or write, but was very street savvy. He had worked as a sharecropper.
- Although he had a good relationship with the staff at the clinic, he mistrusted the medical system with which had a number of "bad experiences".
- There are a number of studies that show that he is not alone in his mistrust.
- It's not just Tuskegee, there is a long hx of pervasive abuse by the medical establishment from slavery, colonialism, exhibitions, involuntary surgeries (Mississippi appendectomy), stealing of bodies for dissection in medical schools, and involuntary experimentation.

*Tuskegee study went from 1932 and ended 1972. CDC website timeline

Colored Entrance to Movie Theater



Colored Waiting Room



Tuskegee Syphilis Study 1932-1972



Timeline of Some Important Dates

- 1863 Emancipation Proclamation ends slavery.
- 1932 Tuskegee syphilis study begins. It does not end until 1972.
- 1947 Jackie Robinson is 1st AA in major league baseball
- 1954 Brown vs Board of Education, Supreme Court rules against school segregation. Overturned separate but equal ruling.
- 1954 our patient is born outside of Mobile, Alabama.
- 1955 Rosa Parks refuses to give up her seat to a white person on a Montgomery, Alabama bus.

Timeline of Some Important Dates

- 1962 James Meredith becomes the 1st AA student to enroll in the Univ. Of Miss. 5000 federal troops are sent to quell violence and riots
- 1963 MLK organizes a march in Birmingham, Alabama, police turn fire hoses and dogs on marchers.
- 1968 Martin Luther King assassinated
- 1972 Tuskegee study ends after 40 years
- 1987 Magic Johnson retires from basketball when he learns he has HIV

Timeline of Some Important Dates

- 1992 Riots in LA after Rodney King beating by police.
- 1996 AIDS becomes the leading cause of death in AA women age 25-44.
- 2000 After massive protests, Gov. of South Carolina removes confederate flag from the dome of the statehouse.

Our Patient's Timeline



National telephone survey of 500 African-Americans aged 15-44 done in 2003

TABLE 2. HIV/AIDS Conspiracy Beliefs Endorsed Overall and by Gender (n = 500)

HIV/AIDS Conspiracy Belief	% Agree Somewhat or Strongly		
	Overall (n = 500)	Men (n = 174)	Women (n = 326)
The medicines used to treat HIV are saving lives in the black community	38.4	42.0	36.5
A lot of information about AIDS is being held back from the public	58.8	62.6	56.8
HIV is a man-made virus†	48.2	48.3	48.2
There is a cure for AIDS, but it is being withheld from the poor	53.4	55.2	52.5
The government is telling the truth about AIDS	37.0	31.6	39.9*
The medicine used to treat HIV causes people to get AIDS‡	6.0	7.5	5.2
HIV was created and spread by the CIA‡	12.0	16.1	9.8†
AIDS is a form of genocide against blacks‡	15.2	20.7	12.3*
The medicine that doctors prescribe to treat HIV is poison‡	6.8	8.6	5.8†
AIDS was created by the government to control the black population‡	16.2	21.3	13.5
Doctors put HIV into condoms‡	1.6	4.0	0.3†
People who take the new medicines for HIV are human guinea pigs for the government‡	43.6	43.7	43.6
Medical and public health institutions are trying to stop the spread of HIV in black communities	75.4	74.1	76.1
AIDS was produced in a government laboratory‡	26.6	30.5	24.5*

Significance values are based on χ^2 tests between women's and men's frequency distributions of the 5 category responses to each item (disagree strongly, disagree somewhat, no opinion/do not know, agree somewhat, agree strongly), $df = 4$.
 * $P < 0.05$.
 † $P < 0.01$.
 ‡Items retained in final scale.
 CIA indicates Central Intelligence Agency.

Bogart LM, Thorburn S. Are HIV conspiracy beliefs a barrier to HIV prevention among African-Americans? JAIDS 2005;35:213-18

“HIV is a disease created by the US government to reduce or wipe out AA population”, 47.2% reported Yes

- A cross sectional survey conducted in 2005 with 466 men aged 18-59. Comprehensive culturally-sensitive and gender-specific survey instrument for the assessment in knowledge, myths and misconception; attitudes; and sexual behavior that act as barriers in HIV prevention, among AA male population living in urban and rural communities of Mississippi.
- Of the respondents 68% were straight, 14.4% bisexual and 16.6%, MSM. Respondents sexual partners in the last 12 months were 1-2 (54%); 3-4 (25.7%); 5 and higher (20.2%) and 55.4% ever had an STD/HIV test. Mean HIV knowledge score was 21.7 (sd±8.9).
- On whether HIV is a disease created by the US government to reduce or wipe out AA population, 47.2% reported yes, 39.7 % (no) and 9.2% (don't know).
- Those who indicated “yes” were more likely to have been involved in the following: a “threesome” sex; exchanged sex for alcohol, drugs or money; had unprotected sex with someone who shoots drugs, used to shoot drugs, or who has had sex with drug user ($p < 0.001$); but less likely to consider HIV testing ($p < 0.001$).

A.Sallar, et al. Are HIV/AIDS conspiracy beliefs barriers to HIV prevention among African Americans men residing in southern United States?. : AIDS 2006 International AIDS Conference: Abstract no. TUPE0620”

How to deal with mistrust

- Establish a relationship with mutual respect.
- Build a therapeutic alliance.
- You must earn their trust
 - Follow through on promises
 - Show care, call to check up how they are doing, home visit?, fill out paperwork, get benefits for them
 - Find out about their life, family, get their story and perspective. “you got to go where he lives”
 - Be open to disagreement over the plan, acknowledge disagreements
- Ask and discuss health care beliefs,.
- Assess their strengths and weaknesses

Building Trust

- Read about and discuss trust with your colleagues and staff. Get culturally competent.
- Arrange for peer to peer counselling, someone who looks like them and knows where they came from.
- Elicit the help of the family or trusted friend, if it is ok with the patient
- Discuss beliefs of experimentation or conspiracy about HIV
- Magic Johnson when he is asked about HIV was made to kill off African Americans answers, if your house is on fire the first thing you have to do it put it out and later figure out how it started. Man made or not you have to deal with HIV.
- Be aware that skepticism may be related to unsafe sexual practices and med nonadherence. Counsel about prevention for positives.
- Do your best, but in the end some may still not take meds

Kleinman Questions can facilitate an understanding of the pt. point of view.

- What do you think caused your problem?
- Why do you think it started when it did?
- How severe is it?
- What do you fear most about your illness?
- What are the major problems your illness has caused?
- What treatments do you think you should receive?

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- Pearl and Peril: if you see someone who has advanced AIDS, knew of their status and never took meds consider a DDX of “Can’t take their pills” and include mistrust on the list to explore.

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My Deepest Thanks

- To my patients from whom I constantly learn
- My colleagues at SFGH Ward 86 and Southeast Heath Center
- The EIP program at SEHC that established a model for reaching African-Americans with HIV who are not in care.
- SFGH Ward 86 Phast program and amazing social services

Questions or comments or would like the slides: dwlodarczyk@php.ucsf.edu

Generic question, I can use later

25% A. Answer a

25% B. Answer b

25% C. Answer c

25% D. Answer d