James Riddell IV, M.D., FIDSA
Clinical Associate Professor
Division of Infectious Diseases
HIV/AIDS Treatment Program
81 year old man

PMH/PSH
- A Fib, CAD
- β Thalassemia
- Dyslipidemia, GIB
- PEs and DVT s/p IVC filter
- C. Diff colitis

Current Meds
- Atenolol 12.5 mg BID
- Ezetimibe-simvastatin 10-40 mg
- Pantoprazole 40mg BID
- Vitamin D3 2,000u daily
- Cyanocobalamin 250 mcg daily
- Folic Acid 400mg daily

FHx
- Mother: MI at 67
- Father: cancer at 79

SHx
- Married for 60 years
- 40 PY history. Quit 2001
- Rare alcohol, Ø illicit drug use

Clinical Course

Oct 10-15/2016
OSH for a GIB
- Gastric ulcer
- Proctitis

Jan 22-25/2017
OSH for shock
- Plt 60-70k
- Cr 1.4

Feb 8 - 9
Nephrologist concerned for vasculitis → UM

Feb 14
Transfer to UM

Jan 26 – Feb 4
OSH for AMS, HCAP
- Plt 66k
- Cr 2.1
- + rheum labs

Feb 12 – Feb 14
OSH for fever, diarrhea
2/14
Transferred to UM

2/15
Tm 39.4, HR 120s
Worsening hypoxia

2/16
Tm 39.3

2/17
Intermittent fevers
Started Solumedrol
Positive Fungitell
Started Voriconazole

2/18 – 2/21
Intermittent fevers
Stable 2L O₂ req

2/21
Renal biopsy done
### Clinical Course – 2/22 (hospital day # 8)

- **Date:** 2/21/2017
- **Result:** Reactive

**HIV ANTGEN ANTIBODY**

<table>
<thead>
<tr>
<th>HIV Antigen Antibody</th>
<th>Result</th>
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<td>Reactive</td>
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**HIV-1 Ab Differentiation**

- **Comments:** Bands detected: gp160, p24, gp41.
- **Presence of HIV-1 antibodies is confirmed.**

**Test Name:** HIV-1 RNA, Quantitative

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<thead>
<tr>
<th>Result</th>
<th>Value</th>
<th>Units</th>
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<tr>
<td>Detected</td>
<td>889263</td>
<td>Copies/mL</td>
</tr>
<tr>
<td>Log10 Copies/mL</td>
<td>5.95</td>
<td></td>
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**CD4, Abs**

- **T-Helper/Inducer:** 66
HIV is Ageless.

Get Tested.

HIV is Ageless.

GMHC
FIGHT AIDS. LOVE LIFE.
“LOTS OF THINGS COME WITH AGE.”

HIV doesn’t have to be one of them.

50

New England Association on HIV Over Fifty (NEAHOF)

In Collaboration with
The New England AIDS Education and Training Center

Presents:
Prevention, Care & Management

5th Annual HIV Over Fifty Update:
Across Communities & Culture
New RFA for 2017

The purpose of this funding mechanism is to promote aging research among the CFAR investigators and engage OAIC researchers in the field of HIV.
Topics of Discussion

- Epidemiology
- Antiretroviral therapy
- Causes of death and life expectancy
- Premature aging
- Pathophysiology of HIV/aging
- Case examples
- Summary and conclusions
Diagnosis of HIV infection by age, 2015 – United States

N = 39,393

<table>
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<tr>
<th>Age at diagnosis (yr)</th>
<th>Diagnoses, %</th>
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<tbody>
<tr>
<td>13–24</td>
<td>22%</td>
</tr>
<tr>
<td>25–34</td>
<td>33%</td>
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<tr>
<td>35–44</td>
<td>19%</td>
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<tr>
<td>45–54</td>
<td>16%</td>
</tr>
<tr>
<td>≥55</td>
<td>9%</td>
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</table>
Diagnosis of HIV infection by age, 2014 – United States
Rates of diagnoses of HIV infection by age 2010-2014, United States
The aging of the HIV epidemic

Number of People Living with HIV

- Age 50 and Older in 2011: 37%
- Age 50 and Older in 2015: 50%
- Age 50 and Older in 2020: 70%

1.25 Million
Cascade of care for HIV infected patients > age 50

- Ages 45-54:
  - Diagnosed: 89%
  - Linked to Care: 75%
  - Retained in Care: 43%
  - Prescribed ART: 39%
  - Virally Suppressed: 31%

- Ages 55-64:
  - Diagnosed: 89%
  - Linked to Care: 74%
  - Retained in Care: 46%
  - Prescribed ART: 42%
  - Virally Suppressed: 36%

- Ages ≥65:
  - Diagnosed: 89%
  - Linked to Care: 73%
  - Retained in Care: 35%
  - Prescribed ART: 33%
  - Virally Suppressed: 27%
Why are older patients at risk for HIV infection?
Why are older adults at risk for contracting HIV?

- Many widowed and divorced people are dating again.
  - May be less aware of their risks for HIV than younger people, believing HIV is not an issue for older people.
  - May be less likely to use barrier protection.
  - Viagra....

- Women who no longer worry about becoming pregnant may be less likely to use a condom and to practice safer sex.

- Older adults visit physicians more frequently, but...
  - Older people are less likely than younger people to discuss their sexual habits or drug use with their doctors.
  - And, health care providers are less likely to ask their older patients about these issues.
Risk factors for HIV transmission
Antiretroviral therapy
<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Presentation</th>
<th>Standard adult dose</th>
<th>Pill by Major side effects</th>
<th>Comments/Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Acetaminophen</td>
<td>Tablet</td>
<td>325 mg, 650 mg, 1000 mg</td>
<td>Headache, nausea, vomiting, diarrhea</td>
<td>Take with food</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Motrin</td>
<td>Tablet, Capsule</td>
<td>50 mg, 100 mg</td>
<td>Headache, nausea, vomiting, diarrhea</td>
<td>Take with food</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Advil</td>
<td>Tablet</td>
<td>200 mg, 400 mg</td>
<td>Headache, nausea, vomiting, diarrhea</td>
<td>Take with food</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Aleve</td>
<td>Tablet</td>
<td>220 mg, 550 mg</td>
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<td>Take with food</td>
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<tr>
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<td>Bayer</td>
<td>Tablet</td>
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<td>Headache, nausea, vomiting, diarrhea</td>
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</tr>
<tr>
<td>Oxycodone</td>
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<tr>
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<td>Vicodin</td>
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<td>Ritalin</td>
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<td>Elavil</td>
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<td>10 mg, 25 mg, 50 mg</td>
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<tr>
<td>Propranolol</td>
<td>Inderal</td>
<td>Tablet</td>
<td>10 mg, 20 mg, 40 mg</td>
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<tr>
<td>Metformin</td>
<td>Glucophage</td>
<td>Tablet</td>
<td>500 mg, 1000 mg</td>
<td>Headache, nausea, vomiting, diarrhea</td>
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<tr>
<td>Statins (lipid-lowering drugs)</td>
<td>Lipitor, Crestor, Vytorin</td>
<td>Tablet</td>
<td>10 mg, 20 mg, 40 mg</td>
<td>Headache, nausea, vomiting, diarrhea</td>
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<tr>
<td>Warfarin</td>
<td>Coumadin</td>
<td>Tablet</td>
<td>5 mg, 10 mg, 20 mg</td>
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</tr>
<tr>
<td>Digoxin</td>
<td>Lanoxin</td>
<td>Tablet</td>
<td>0.125 mg, 0.25 mg, 0.5 mg</td>
<td>Headache, nausea, vomiting, diarrhea</td>
<td>Take with food</td>
</tr>
<tr>
<td>Insulin</td>
<td>Humalog, Novolog</td>
<td>Injection</td>
<td>Unit dose</td>
<td>Headache, nausea, vomiting, diarrhea</td>
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<tr>
<td>Oral contraceptives</td>
<td>Ortho Tri-Cyclen, Truvada</td>
<td>Tablet</td>
<td>0.03 mg, 0.05 mg</td>
<td>Headache, nausea, vomiting, diarrhea</td>
<td>Take with food</td>
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<tr>
<td>Prednisone</td>
<td>Pred Forte</td>
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<td>5 mg, 10 mg, 20 mg</td>
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<td>Levothyroxine</td>
<td>Synthroid</td>
<td>Tablet</td>
<td>50 mcg, 100 mcg</td>
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<td>Amoxicillin</td>
<td>Augmentin</td>
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<td>Metronidazole</td>
<td>Flagyl</td>
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<td>250 mg, 500 mg</td>
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<td>Imodium A-D</td>
<td>Loperamide</td>
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<td>Colace</td>
<td>Tablet</td>
<td>75 mg</td>
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<tr>
<td>Chlorpheniramine</td>
<td>Allergy Medicine</td>
<td>Tablet</td>
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HIV related AIDS diagnoses and Deaths
Management issues in older HIV infected patients

- Age related loss of renal and/or hepatic function – changes metabolism of drugs
- Drug-drug interactions (P450):
  - Statins, amiodarone, anticonvulsants, inhaled corticosteroids
- Older age groups excluded from drug development trials
  - Pharmacokinetic data is lacking
  - Drug toxicities
HAART adherence improves with age

Hinkin, AIDS, 2004
Increase in CD4 stratified by age 2 years after HAART

Althoff, IEDEA, 2/2010
Immunosenescence

• Immune system in aged (> 70 y/o)
  – Increased terminally differentiated CD8 cells (cytotoxic T-cells)
  – Reduced level of naïve CD8 cells
  – Increased T-cell activation
  – Increased levels of inflammatory markers
  – Reduced T-cell proliferation

• All accelerated with chronic infection
Aging and complications of antiretroviral therapy

• Chronic adverse effects related to HAART:
  – Increased CAD risk
  – Metabolic abnormalities: hyperlipidemia, glucose intolerance

• Conditions seen at earlier age
  – Osteoporosis
  – hypogonadism
HIV+ Patients Still Have a 10y Shorter Life Expectancy than HIV- Controls

Survival from Age 25 Years
N= 3,990

Probability of Survival

Age, years


(See Also: ART-CC, Lancet, 2008; Lewden, JAIDS, 2007)
Life expectancy

HIV Medicines Help People with HIV Live Longer
(AVERAGE YEARS OF LIFE)

- A person without HIV: 79 YEARS
- A person with HIV diagnosed at age 20 taking current HIV medicines: 71 YEARS
- A person with HIV diagnosed at age 20 not taking current HIV medicines: 32 YEARS

Life expectancy for a 20 year old initiating ART

By pre-ART CD4 count

- ≥ 350
- < 350

Years


Proportion surviving after AIDS diagnosis by age group 1997-2004
Cause of death according to time since start of ART

The chart illustrates the crude rate per 1000 person years for various causes of death among HIV-positive individuals, categorized by time since start of ART (Antiretroviral Treatment) as follows:

- **< 1 year**
- **1-2 years**
- **> 2 years**

The causes of death include:

- AIDS
- Non-AIDS Malignancy
- Non-AIDS Infection
- CVD
- Violent deaths
- Liver related
- Respiratory disease
- Renal failure
- Other causes (N<20)

The chart highlights that AIDS is the leading cause of death, with the highest crude rate, followed by Non-AIDS Malignancy and Non-AIDS Infection.
Cumulative incidence of AIDS and non-AIDS related deaths
Non-AIDS deaths after entering care

Braithwaite, Am J Med, 2005
Premature aging comorbidities common in patients with HIV

- Diabetes
- Cardiovascular disease
- Cancer
- Renal dysfunction
- Cognitive dysfunction
- Osteoporosis
- Low testosterone
Residual Viral Replication
Persistent virus expression (in LN)
Collagen Deposition
Mircrobial Translocation
High pathogen load (CMV, HCV)
Thymic dysfunction

Suboptimal CD4 Gains
Residual Inflammation
Immuno-senescence

Non-AIDS Events and Premature Mortality

Adapted from Hsue CROI 2010
Natural history of suppressed viremia
Inflammatory Biomarkers and Mortality Risk Among HIV-Suppressed Men: A Multisite Prospective Cohort Study
Argument for starting antiretroviral therapy in all patients

• Inflammation associated with viral replication
  – Higher levels of inflammatory markers
  – Increased risk of clotting
  – Poor endothelial function

• Increased risk of vascular disease if treatment is delayed with associated end organ damage
Argument for starting antiretroviral therapy in all patients

- Malignancy
  - Non-AIDS related cancers more commonly associated with HIV infection
  - Lower CD4, increased risk for cancers
  - CD4 > 500, antiretroviral therapy seems to be protective (in some studies)
Colon Cancer screening

Prevalence of lesions in HIV infected patients versus controls

Bini, Gut 2009;58:1129-1134
Case #1

A 50 y/o man presents with a new diagnosis of HIV infection with and a CD4 count of 235 and a viral load of 35,280. He is initiated on a regimen consisting of tenofovir/emtricitabine and lopinavir/ritonavir. He responds with an increase in his CD4 count and undetectable viral load after 3 months. Baseline fasting lipid profile is unremarkable.
A routine screening cholesterol profile is obtained 3 months later and reveals:

Triglycerides – 550
HDL – 32
LDL - 235
Options for treatment: Elevated triglycerides

- Initiate TG lowering therapy (>500)
  - Fenofibrate (Tricor)
  - Gemfibrozil (Lopid)
  - Niacin
  - Fish oil

- Change antiretrovirals
  - Different PI
  - Different class (NNRTI)

Change in Triglycerides: Week 0 to Week 48

**Maggiolo et al. 6th International Congress on Drug Therapy in HIV Infection, Glasgow, UK, 2002.**

![Graph showing the change in triglycerides from Week 0 to Week 48. The graph compares two groups: Maintain PI and Switch to NVP. The y-axis represents mg/dL, and the x-axis represents months. The graph shows a significant increase in triglycerides for the Maintain PI group and a decrease for the Switch to NVP group. Significant differences are indicated at weeks 4, 8, and 12 with *P<0.05.*]
Drug Interactions: Statins and PIs - ACTG 5047

- HIV-negative adults received ritonavir + saquinavir on days 5-18, and pravastatin, simvastatin, or atorvastatin on days 1-4 and 15-18. pK analyses performed on days 4 and 18

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Day 4</th>
<th>Day 18</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>14</td>
<td>71.9</td>
<td>283.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>14</td>
<td>17.1</td>
<td>548.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>14</td>
<td>143.5</td>
<td>93.3</td>
<td>.05</td>
</tr>
</tbody>
</table>

Fichtenbaum et al; AIDS 2002.
• Prospective observational study of 23,468 patients over 1.6 years follow up

• Longer exposure to HAART – Increased incidence of MI adjusted RR/yr exposure = 1.26

• Traditional risk factors also associated: DM, hyperlipidemia, smoking, older age, male sex
CAD risk in HIV infection:

**Observed and predicted MI rates according to ART exposure**
(D:A:D Study; n=23,468)

Incidence of MIs is low: 345 over 94,469 patient-years’ follow-up (3.7/1,000 patient-years)

<table>
<thead>
<tr>
<th>Duration of cART Exposure (Years)</th>
<th>None</th>
<th>&lt;1</th>
<th>1–2</th>
<th>2–3</th>
<th>3–4</th>
<th>4+</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=ART exposure</td>
<td>5,973</td>
<td>5,292</td>
<td>6,805</td>
<td>9,050</td>
<td>10,574</td>
<td>8,890</td>
</tr>
</tbody>
</table>

Risk/Benefit Analysis of CAD and HAART

Average calculated increase in CAD events = 0.14% per year

Risks

↓ Mortality rates in HIV-infected patients by 50% in the US

Benefits

Adapted from Grunfeld. 6th CROI; 1999; Chicago. Palella. NEJM 1998;338:853.
Case #2

52 y/o man who is taking tenofovir/emtricitabine, and ritonavir boosted darunavir presents with complaints of worsening left hip pain which has been present for 2-3 months. An x-ray of the hip was normal. His symptoms have been refractory to NSAIDs and physical therapy.
Avascular necrosis of the femoral head
HIV associated osteonecrosis

• Has been identified as a complication of HIV infection since the 1980’s
• Screening study – 15/339 (4.4%) were found to have avascular necrosis of the hip by MRI
  – Risk factors: corticosteroid use, hyperlipidemia, exercise, not specific antiretrovirals
HIV associated osteonecrosis

• Routine screening not recommended
• In symptomatic patients diagnosis may be made by X-ray or more commonly MRI of involved joint
• Treatment limited to management of symptoms and joint replacement
  – Attempt reversal of any risk factors identified

Schambelan, JAIDS 2002,31:257-275
Bone mineral density comparison

Yin et al, 2005
Teichman et al, 2003
Tebas et al, 2000
Madeddu et al, 2004
Loiseau-Peres et al, 2002
Knobel et al, 2001
Huang et al, 2002
Dolan et al, 2004
Bruera et al, 2003
Brown et al, 2004
Amiel et al, 2004

HIV-positive
HIV-negative

Brown TT, AIDS 2006;20:2165-74
Osteoporosis and HIV infection

Overall prevalence: 15%

Causes for osteoporosis/osteopenia

- Vitamin D deficiency
- Hypogonadism
- Hypothyroidism
- Medications
  - Sustiva linked to Vit D deficiency
  - Tenofovir linked to bone mineral abnormalities
Tenofovir phosphate taken up by osteoclasts: Toxicity

- Decreased osteoblast activity
- Increased osteoclast activity

Grigsby, Ther Clin Risk Manag, 2010
HIV in older population, Summary:

<table>
<thead>
<tr>
<th>Category</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence</td>
<td>Older &gt; Younger</td>
</tr>
<tr>
<td>Viral load suppression</td>
<td>Older &gt; Younger</td>
</tr>
<tr>
<td>CD4 increase</td>
<td>Younger &gt; Older</td>
</tr>
<tr>
<td>Morbidity + Mortality</td>
<td>Older &gt; Younger</td>
</tr>
</tbody>
</table>
Conclusions

• Patients with HIV are living longer because of HAART
• Older patients can become HIV infected!
• Patients on HAART long term are at higher risk for CAD
• Need to be aware of risk for osteoporosis, hyperlipidemia
• Standard screening applies to older patients with HIV infection