Preventative Management for HIV Infected Persons

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Learning Objectives
Upon completion of this presentation, learners should be better able to:

• Identify and use appropriate guidelines to conduct preventative management for HIV-infected persons
• Apply updated guidelines for CD4 and VL monitoring
• Monitor for and manage CKD in HIV-infected patients
• Assess for and manage smoking cessation and lung cancer screening.
• Not meant to be an exhaustive reference for HIV-related primary care! (See Aberg CID Nov 15th 2013)
Faculty and Planning Committee Disclosures

Please consult your program book.

Off-Label Disclosure

There will be no off-label/investigational uses discussed in this presentation.
Case: H.E.

- 50 yo African American man
  - Presented to San Francisco General Hospital with one month of shortness of breath, cough, fevers, rigors, chills, and 30 lb wt loss.
  - Diagnosed with PCP, pulmonary MAC
  - New dx HIV, CD4 71
## Baseline Testing Highlights

<table>
<thead>
<tr>
<th>Test</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Serology, CD4, Viral Load</td>
<td>If not yet done</td>
</tr>
<tr>
<td>HIV resistance testing</td>
<td>Transmitted drug resistance in 6-16% *INSTi resistance has been reported</td>
</tr>
<tr>
<td>Tropism assay</td>
<td>Only if use of CCR5 antagonist considered</td>
</tr>
<tr>
<td>HLA B*5701</td>
<td>For abacavir hypersensitivity</td>
</tr>
<tr>
<td>Chemistries, lipids, CBC</td>
<td>Renal function, lipid mgmt, anemia/thrombocytopenia</td>
</tr>
<tr>
<td>Hep serologies</td>
<td>Vaccination and/or treatment</td>
</tr>
<tr>
<td>Pap Smears</td>
<td>Cervical, anal</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Proteinuria, hematuria</td>
</tr>
<tr>
<td>STD Screen</td>
<td>Syphilis, gonorrhea, chlamydia, trichomonas</td>
</tr>
<tr>
<td>VZV, toxo, TB screen</td>
<td>Vaccination, prevention, LTBI</td>
</tr>
</tbody>
</table>
Clinical follow-up

- Genotype sent, started on DRV/r, TDF/FTC
- PMH: notable for 40 py tobacco history
- At 2\textsuperscript{nd} visit, “Doctor J: you told me HIV weakens my immune system. What does that mean?”
What vaccines should we *not* offer this 50 yo HIV+ patient (CD4 ~73)?

1. Pneumococcal vaccine(s), Hep B
2. Tetanus/Diphtheria/Pertussis, Hep A, inactivated flu
3. Varicella, Live attenuated influenza (flumist)
4. Human Papilloma Virus, Herpes Zoster (Shingles)
5. 3 and 4
HIV-specific issues with vaccines

- Measured immune response is not as robust in HIV-infected versus HIV-uninfected for many vaccines
- Except for seasonal and travel vaccines, try to give when CD4 count > 200 cells / μL, if increase is expected
Vaccines currently contraindicated in HIV

- Live attenuated intranasal influenza (LAIV, Flumist)
- Oral polio virus (OPV)
- Smallpox
- Typhoid oral vaccine (Ty21a)
- Bacillus calmette-guerin (BCG)
Vaccines with special precautions for HIV-Infected

Live vaccines that are okay when CD4 count > 200 cells/μL
• Measles/mumps/rubella (MMR)
• Varicella (VARIVAX)
  – Two doses if not immune
• Zoster (ZOSTAVAX)
  – For age ≥ 60 years
• Yellow fever
  – Caution with CCR5 inhibitors – based on worse disease outcomes of flavivirus infections in persons with CCR5 receptor mutations, especially West Nile virus
• http://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html
A few specifics: Pneumococcus

- Persons with HIV have ~ 35-fold increased risk of invasive pneumococcal disease compared with age-matched controls in 2000
  
  Heffernan et al; J Infect Dis 2005

- U.S. study showed lower rates pneumococcal disease in vaccinated persons with CD4 count > 500 compared with unvaccinated
  
  Dworkin et al; Clin Infect Dis 2001

- Uganda study showed excess all-cause pneumonia with vaccine (HR=1.6) but decreased all-cause mortality (HR=.84)
  
  Watera et al; AIDS 2004
Pneumococcal Polysaccharide Vaccine in HIV – PPSV23

• CDC guidelines published 1997
  – For HIV-infected adolescents and adults: vaccinate at time of diagnosis; single booster after 5 years; vaccinate x 1 after age 65, provided at least 5 years have elapsed since last vaccine
• Revaccination every 5 years has been advocated by some; consider revaccination when CD4 count ≥ 200 cells/μL
  – 2013 guidelines for prevention and treatment of OIs now agree with CDC guidelines
• Worse initial serologic response to vaccine with HIV and vaccine does not boost well in general
Pneumococcal 13-Valent Conjugate Vaccine for Adults

• Clinical trial in the Netherlands: 85,000 adults ≥ 65 randomized to PCV13 vs. placebo – (CAPiTA trial)
  – 46% fewer first cases of vaccine type pneumococcal CAP – primary outcome
  – 75% fewer first cases vaccine type invasive pneumococcal disease

• 2011: U.S. FDA and European Commission approved vaccine for adults 50 and older

• 2012: Recommended by Advisory Committee on Immunization Practices (ACIP) / CDC for selected adults, including those with HIV
Which pneumococcal vaccine do I give first?

- For HIV-infected adults who have not received pneumococcal vaccine, administer PCV13 first, then PPSV23 6-12 months later
  - Minimum interval 8 weeks
- If previously vaccinated with PPSV23, give PCV13 at least one year after PPSV23

*MMWR* 2014;63(37):822-25.
HIV and Human papilloma virus

• In HIV+ compared with HIV neg MSM, HPV prevalence in anal canal higher, high risk types higher, and anal intraepithelial neoplasia more likely
  – Anal cancer incidence estimated to be at least 2X higher
• Cervical intraepithelial neoplasia rate 4-5x higher in HIV+ compared with HIV neg women and girls
  – Persistent infection with HPV is more likely
  – Based on data from 1990s to early 2000s
  – HIV is a risk factor for anal intraepithelial neoplasia in women
• Low CD4 count risk factor for intraepithelial neoplasia
  – Studies on effect of ART inconsistent

Crum-Cianflone NF AIDS 2010
HPV Prevention: Vaccines

- 2006: Quadrivalent HPV vaccine (Gardasil) FDA approved
  - Major capsid protein L1 from types 6,11,16, 18
- 2009: Bivalent vaccine against types 16/18 (Cervarix) for girls and women age 10 – 25 in 2009
- 2010: FDA approved Gardasil for prevention of anal cancer and precancerous lesions in persons ages 9 – 26 based on data from HIV-negative MSM
- Both vaccines immunogenic in females and males
  - Excellent short-term efficacy (nearly 100%) in preventing infection with HPV types included in vaccine, if not previously infected

Palefsky et al, NEJM 2011
HIV and HPV vaccines

• Trials enrolling to date have included immunogenicity, safety, tolerability, and behavioral endpoints
  – Gardasil safe and immunogenic in HIV-infected men, women, and HIV-infected children
  – Cervarix may induce better vaccine response than Gardasil in HIV-infected women
  – Although efficacy data not yet available, ACIP recommends HPV vaccine for all HIV infected boys and girls at ages of 11 or 12. Also recommended in those aged 13 through 26 who did not get any or all doses when they were younger

Wilkin et al; J Infect Dis 2010
Kahn JA; Clin Infect Dis. 2013
Toft et al; J Infect Dis 2014
Levin et al; JAIDS 2010
Kim et al; Ann Intern Med 2015
How do I prevent anal cancer in my 50 y/o HIV-infected patient?

• Annual screening for anal dysplasia by DRE and anal PAP (if available)
  – If abnormal, follow with high-resolution anoscopy with biopsy of abnormal areas, then appropriate treatment
  – Annual screening recommended for MSM, women w/ history of receptive anal intercourse or abnl cervical PAP results, and all HIV-infected persons with genital warts
    • Guidance extrapolated from high risk of anal neoplasia in HIV-infected and efficacy of screening for cervical CA
    • Ongoing study of efficacy of anal dysplasia surveillance (ANCHOR, PI Palefsky)

Aberg et al CID 2013
Clinical follow-up

- Given PCV13, PPSV23, Hep B, Hep A, TDAP, and Flu vaccines
- Multiple anal warts on physical exam, treated with LN
  - Anal pap without dysplasia
- 100% adherence to his meds, quickly suppressed, but …
- Delayed CD4 recovery
  - Every visit: “Doctor J: What’s my T cell count?”
Case: Poor initial CD4 recovery

Graph showing HIV viral load and CD4 count over time from 7/1/11 to 8/2/12.
Warm-up: How often should we check his CD4 count?

1. Every 3-4 months
2. Every 3-4 months until his CD4 is >300
3. Every 6 months
4. Every year
5. Less frequent
6. I don’t know
Consequences of poor CD4 response?

• Associated with increased non-AIDS mortality and morbidity among virologically suppressed patients
• But... Can we do anything with this information?
  – IL-2 raised CD4 counts, but no reduction in death/OI risk
  – Treatment intensification, CMV treatment not associated with CD4 recovery
  – Increasing evidence that phenotype related to increased immune activation/microbial translocation
Revised May 2014: “Measurement of CD4 count is particularly useful before initiation of ART. A repeat CD4 count 3 months after ART initiation will provide information regarding the magnitude of immune reconstitution... in the first 2 years following ART initiation, CD4 count can be monitored at 3-6 month intervals.”
Case: Eventual, delayed recovery after 1 one year
Now: How often should we check his CD4 count?

1. Every 3-6 months
2. Every 6-12 months
3. Every year
4. No more! Stop the CD4 madness!
5. I don’t know
“For patients on suppressive ART regimens whose CD4 counts have increased well above the threshold for opportunistic infection risk, the CD4 count can be monitored every 6–12 months”
In patients with consistently suppressed viral loads who have already experienced ART-related immune reconstitution, the CD4 count provides limited information.”

“After 2 years of ART:

- VL suppressed, CD4 300-500: every 12 months
- VL suppressed, CD4 >500: OPTIONAL
Summary: CD4 monitoring

- Consider monitoring every 3-4 months when CD4 count <200 to gauge when to stop PCP prophylaxis
  - But, risk is very low in virally suppressed. 0%?
- Once ≥300-500 and/or ≥14%, if VL is consistently suppressed:
  - Check annually
- Once ≥500
  - Optional! (aka if it makes you or your patient feel better)
- What about CD8 T cells and other subsets?
  - No clinical utility. And expensive! Not recommended
VL Monitoring: 2014 DHHS and 2013 Primary Care Guidelines

- 2-8 weeks after initiation of ART
  - Every 4-8 weeks until suppressed
- First 2 years of ART: Every 3-4 months
- After 2 years of ART with consistently suppressed VL: Every 6 months
- At treatment failure or when “clinically indicated”
  - Along with repeat resistance testing

Aberg et al CID 2013
DHHS Guidelines 2014
Primary care course cont..

- Creatinine transiently bumped from 0.9 to 1.4 two months after starting ART
- Repeat Cr 1.1 two wks later (GFR >60)
- UA at diagnosis: 1+ protein, otherwise unremarkable. No diabetes
- On DRV/r, TDF/FTC
How would you manage his renal issues at this point?

1. Monitor: Q6 month renal panel + UA
2. Monitor: Q12 month renal panel + UA
3. Monitor AND Discontinue his tenofovir
4. Monitor AND Discontinue his TDF and PI
5. Monitor and start an ACE-I
6. Something else
Why care about CKD in HIV-infected individuals?

- Decreased GFR and albuminuria associate with higher mortality in HIV-infected individuals.
- Increased incidence of acute kidney injury in HIV-infected individuals (incidence 2.8-5.9/100 py).
  - AKI in HIV associated with increased risk and severity of heart failure, CV events, ESRD.

Lucas et al CID 2014
Choi AI et al. Kindey Int 2010; 78:478-85
Wyatt JAIDS 2010; 55:73-7
Diagnosing CKD: not just GFR

## Risk factors for CKD in HIV

<table>
<thead>
<tr>
<th>Factor</th>
<th>CKD Relative Risk Range</th>
<th>ESRD Relative Risk Range</th>
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</thead>
<tbody>
<tr>
<td>African descent</td>
<td>1.7-2.4</td>
<td>4.5-31</td>
</tr>
<tr>
<td>Female Sex</td>
<td>1.5-1.7</td>
<td>NR</td>
</tr>
<tr>
<td>Age</td>
<td>1.2-5.5 per 10y older</td>
<td>2.0 for age &gt;50 vs &lt;30</td>
</tr>
<tr>
<td>CD4 Cell Count</td>
<td>1.4-2.2 for CD4 &lt;200 vs &gt;=200</td>
<td>1.4-2.7 for CD4 &lt;200 vs &gt;=200</td>
</tr>
<tr>
<td>HIV RNA</td>
<td>1.3-2.2 for detectable VL</td>
<td>2.0 per log10 increase VL</td>
</tr>
<tr>
<td>HCV/IVDU</td>
<td>1.3-2.2</td>
<td>2.8-5.0</td>
</tr>
<tr>
<td>TFV</td>
<td>1.2-1.3 per yr of exposure</td>
<td>1.6-2.2 for any vs. no</td>
</tr>
<tr>
<td>TFV + boosted PI</td>
<td>3.4 vs NNRTI-based regimen without tenofovir</td>
<td>NR</td>
</tr>
</tbody>
</table>

Lucas et al CID 2014
Finally: Guidelines!

- Check Cr (and GFR) when ARVs started or changed, and then **q6 months**
  - More frequent for patients with addnl risk factors
- Monitor with urinalysis OR quantitative albuminuria/proteinuria when ARVs started or changed, and then **q12 months**
Back to the case...

- Q6 month creatinine stable between 1.1-1.4
- 12 months later:
  - 1+ urine protein -> 2+
How would you manage his renal issues at this point?

1. Cont monitoring and work-up the proteinuria
2. Do work-up and DC TDF
3. Do work-up and start an ACE-I
4. Do work-up, DC TDF, and start an ACE-I
5. Something else
What about Tenofovir (disoproxil-fumarate)?

- Associated with proximal tubule dysfunction/fanconi’s syndrome
  - Aminoaciduria, Phosphaturia, Glucosuria
- TDF PK associated with concomitant drug
  - unboosed ATZ and boosted PIs = ↑ levels
- Reductions in GFR of 5-10 ml/min/1.73m² (Clinical trials typically excluded individuals with baseline Cr >1.5 or CrCl <60)
- Proteinuria (can precede GFR reductions)

Kelly et al AIDS 2013
Increased incidence of GFR <90 with TDF

Adjusted HR 1.63

Laprise et al. CID 2013
## TDF compared to other ART

<table>
<thead>
<tr>
<th>Antiretroviral</th>
<th>Proteinuria</th>
<th>Rapid Decline</th>
<th>Chronic Kidney Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>P</td>
<td>HR</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>1.34</td>
<td>&lt;0.0001</td>
<td>1.11</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>0.98</td>
<td>0.50</td>
<td>1.02</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>1.18</td>
<td>&lt;0.0001</td>
<td>0.96</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>0.93</td>
<td>0.34</td>
<td>1.22</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>0.77</td>
<td>&lt;0.0001</td>
<td>1.05</td>
</tr>
</tbody>
</table>

Scherzer et al. AIDS 2012
Guidelines: Who should not get/stop TDF?

- Patients with GFR <60 should not receive TDF
  - If other options not optimal (i.e. concurrent HBV), close monitoring

- In TDF-treated patients with GFR decline >25% and to a level <60, discontinue TFV
  - Particularly if evidence of proximal tubule dysfunction or worsening proteinuria

Lucas et al. CID 2014
Guidelines: ACE-i

- Reducing proteinuria shown to reduce rates of progression of kidney disease in diabetic AND non-diabetic patients

- **Who should get an ACE-i or ARB?**
  - Patients with HIVAN (suspected or confirmed)
  - Clinically significant albuminuria
    - >30 mg/day in diabetic patients
    - >300 mg/day in nondiabetic patients
    - If you can’t calculate a 24 hour urine: Calculate a spot Urine Protein or albumin:Creatinine ratio
Back to the case...

- Spot urine pr 200 mg/dl, urine cr 165.7 mg/dl
  - UPCR = 1.21 (nl <0.2)
  - ANA, C3, C4, SPEP, UPEP neg
  - Started on benazepril
  - Referred to renal
- Follow-up safety labs scheduled but patient missed appt
Uh oh..

• Came in 4 weeks later: Cr 14!
  – nl urinary output, no symptoms
• Admitted, ARVs, benazepril held
• Labs: glucosuria, aminoaciduria, phosphaturia -> proximal tubular dysfunction
Could this have been prevented?

• ART options in setting of reduced GFR or worsening proteinuria:
  – Initiate or switch to antiretroviral associated with decreased renal toxicity: ABC/3TC
    • But: Competing risk of cardiac toxicity with ABC? (D:A:D, NA-ACCORD)
  – Reduce TDF dose or frequency of administration
  – Switch off boosted PI (RAL, DTG)
  – Next gen prodrug (tenofovir alafenamide = TAF)
    • Lower plasma TFV levels, smaller decreases in eGFR, less proteinuria

Sax et al CROI 2014
Pozniak et al CROI 2014
Case f/u ...

- Switched to DRV/r, ABC, 3TC
- Had fast recovery of renal function w/ slight ↓ GFR
- Studies: 59% with full recovery

Bonjoch et al Antivir Res 2012
Summary: HIV and renal function

- Monitor Cr/GFR every 6 months and quantitative urine protein every 12 months

- TDF: ↑risk of proteinuria, CKD, and rapid GFR loss
  - Proteinuria may precede GFR declines
  - Avoid TDF in patients with GFR <60
  - Stop TDF in patients with GFR decline >25% and drop to GFR <60
  - Ace-I for individuals with significant albuminuria

- But need to monitor!
What about his 40 py smoking history?

1. Have him call 1-800 -NoBUTTS
2. Counsel him myself
3. Refer to smoking cessation group
4. Offer a nicotine patch
5. All of the above
6. Above AND offer Bupropion SR (Wellbutrin)
7. Above AND offer Varenicline
Smoking in HIV-infected individuals?

• Prevalence in HIV-infected: 40-70%
  – General population prevalence 20%
  – HIV-infected also significantly less likely to quit

• Several studies link smoking in PLWHA to:
  – Decreased virologic/immunologic response
  – Worse adherence to ART
  – Increased rates of non AIDS-defining malignancies (lung, head/neck)
  – Low BMD, CAD, pneumonia

Mdodo et al Ann Intern Med. 2015
Sigel et al AIDS 2012
Stead et al Cochrane Reviews 2012
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Dosing</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>The 5 A’s</td>
<td>Ask, Advise, Assess readiness, Assist, Arrange follow-up</td>
<td></td>
<td>3 minute in clinic behavioral intervention</td>
</tr>
<tr>
<td>Nicotine Patch</td>
<td>&gt;10 cigs/day: 21 mg/day X 6 wks then 14 mg/day X 2wks then 7 mg/day X 2wks</td>
<td>Local skin rxn insomnia</td>
<td>OTC</td>
</tr>
<tr>
<td>Combo NRT better than patch alone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion SR</td>
<td>150 mg qd X 3d then 150 mg bid for 7-12 weeks</td>
<td>Insomnia, dry mouth, HA, tremors, anxiety</td>
<td>Begin 1-2 weeks before quit date</td>
</tr>
<tr>
<td>Varenicline</td>
<td>0.5 mg qd X 3d Then 0.5 mg BID X 4d then 1 mg bid for 12 wks-6 mos</td>
<td>Nausea, HA, sleep disturbance, vivid dreams; depression; suicidal ideation; and suicide</td>
<td>Black Box: Use with caution in patients with history of psychiatric illness. Monitor closely for mood and behavior changes. Dosage reduction recommended for patients who have creatinine clearance (CrCl) of &lt;30 mL/min or are on dialysis.</td>
</tr>
</tbody>
</table>
Our patient

• First offered counseling, nicotine patches
  – No change

• 2 months later: set a start date, started bupropion XL 150 mg daily X 3 days then BID
  – Says he got “jittery” and increased his smoking to 1 ppd!

• 2 months later: started varenicline 0.5 mg qd X 3 days, 0.5 bid X 4 days, then 1 mg bid
  – Cut down smoking over first two weeks, then had absolutely no desire to smoke and quit!
Cochrane meta-analysis of pharmacologic interventions for smoking cessation: 2013

- Bupropion vs NRT
- Varenicline vs NRT
- Varenicline vs Bupropion
- Varenicline vs Combo NRT

Cahill et al Cochrane Library 2013

ACTHIV 2015: A State-of-the-Science Conference for Frontline Health Professionals
The future is here?

- Algorithm-based pharmacotherapy of tobacco in HIV clinics
  - Cropsey et al JAIDS 2015: Randomized trial of algorithmic approach vs standard of care
  - Research staff with no specific prior training in tobacco cessation administered questionnaire and assessed patient’s readiness to quit
  - If patient ready, algorithmic approach of medications (varenicline if no renal failure; then wellbutrin; then NRT)
  - Results: more quit attempts, greater smoking reduction, more cessation readiness
Lung cancer screening is now USPSTF recommended

- Low-dose CT screening
  - 20% reduction in lung cancer mortality
  - 6.7% decrease in all cause mortality
    - Screening 256 persons annually for three years prevents one lung cancer death over six years
- Annual screening for high risk individuals (ages 55-80 and 30 PYH) now Grade B recommendation by USPSTF
  - Also recommended by ATS, ACS, NCCN
## Health care maintenance: other highlights

<table>
<thead>
<tr>
<th>Test</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digital rectal exam</td>
<td>Consider annually in all patients for anal warts, malignancy</td>
</tr>
<tr>
<td>Ophthalmologic exam</td>
<td>Q 6-12 months in patients with CD4 &lt;50; every 2-3 yrs in patients older than 50</td>
</tr>
<tr>
<td>Depression/substance screen</td>
<td>At least annually; consider each visit</td>
</tr>
<tr>
<td>HbA1C, lipids, BP</td>
<td>Q6-12 months</td>
</tr>
<tr>
<td>STD Screen (RPR, GC/CT; trichomoniasis in women)</td>
<td>Q6-12 months</td>
</tr>
<tr>
<td>Cervical Pap smear</td>
<td>Annually in all women after 2 normal Paps documented in first year of diagnosis*</td>
</tr>
<tr>
<td>Colo/Mammo</td>
<td>&gt;50 yrs of age</td>
</tr>
<tr>
<td>Bone densitometry</td>
<td>Postmenopausal women; men &gt;50 yrs of age</td>
</tr>
<tr>
<td>TST or IGRA (Quantiferon)</td>
<td>At baseline and annually</td>
</tr>
<tr>
<td>Hep C testing</td>
<td>Annually in patients at risk (IVDU, MSM)</td>
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<tr>
<td>Abdominal ultrasound</td>
<td>Once in men aged 65-75 who have smoked</td>
</tr>
</tbody>
</table>
Recap: HIV Primary care is tough!

- HIV primary care guidelines (Aberg CID 2013) excellent resource!
- ACIP guidelines for vaccination schedules in HIV-infected
- Annual anal dysplasia screening recommended for nearly all HIV-infected persons
- CD4/VL monitoring in virally suppressed, clinically stable patients
  - CD4 annually when CD4 $\geq 300-500$; Optional once $\geq 500$
  - VL Q3-4 months for first 2 years of therapy, then q6 mos
Recap: Primary care is tough!

- Renal monitoring:
  - Cr/GFR q6 mos; quantitative urine protein q12 months
  - Avoid TDF in patients with GFR <60
  - Stop TDF in patients with GFR decline >25% and drop to GFR <60
  - Ace-I for individuals with significant albuminuria

- Smoking cessation: you have options!
  - Bupropion, nicotine replacement work and have similar efficacy; Varenicline is more efficacious but must consider adverse effects
  - Consider lung CA screening in your older smokers
Thanks!

- Meg Newman, M.D.
- Annie Luetkemeyer, M.D.
- Monica Gandhi, M.D.
- Lisa Winston, M.D.
- Cait Koss, M.D.
- Carina Marquez, M.D.
Extra Slides
### Figure 2. Vaccines that might be indicated for adults based on medical and other indications

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>INDICATION</th>
<th>Pregnancy</th>
<th>Immuno-compromising conditions (excluding human immunodeficiency virus [HIV])</th>
<th>HIV infection (CD4+ T lymphocyte count)</th>
<th>Men who have sex with men (MSM)</th>
<th>Kidney failure, end-stage renal disease, receipt of hemodialysis</th>
<th>Heart disease, chronic lung disease, chronic alcoholism</th>
<th>Asplenia (including elective splenectomy and persistent complement component deficiencies)</th>
<th>Chronic liver disease</th>
<th>Diabetes</th>
<th>Healthcare personnel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza*</td>
<td></td>
<td>1 dose IIV annually</td>
<td>1 dose IIV or LAIV annually</td>
<td>1 dose IIV annually</td>
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<tr>
<td>Tetanus, diphtheria, pertussis (Td/Tdap)*</td>
<td></td>
<td>1 dose Tdap each pregnancy</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Varicella*</td>
<td>Contraindicated</td>
<td>2 doses</td>
<td>3 doses through age 26 yrs</td>
<td></td>
<td>3 doses through age 26 yrs</td>
<td></td>
<td>3 doses through age 21 yrs</td>
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<tr>
<td>Human papillomavirus (HPV) Female*</td>
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</tr>
<tr>
<td>Human papillomavirus (HPV) Male*</td>
<td></td>
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<tr>
<td>Zoster</td>
<td>Contraindicated</td>
<td>1 dose</td>
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<tr>
<td>Measles, mumps, rubella (MMR)*</td>
<td>Contraindicated</td>
<td>1 or 2 doses</td>
<td></td>
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<tr>
<td>Pneumococcal 13-valent conjugate (PCV13)*</td>
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<tr>
<td>Pneumococcal polysaccharide (PPSV23)*</td>
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<tr>
<td>Meningococcal*</td>
<td></td>
<td>1 dose</td>
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<tr>
<td>Hepatitis A*</td>
<td></td>
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<td></td>
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<tr>
<td>Hepatitis B*</td>
<td></td>
<td>2 doses</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Haemophilus influenzae type b (Hiib)*</td>
<td></td>
<td>3 doses</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>post-HSCT recipients only</td>
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</tbody>
</table>

*Covered by the Vaccine Injury Compensation Program

For all persons in this category who meet the age requirements and who lack documentation of vaccination or have no evidence of previous infection, zoster vaccine recommended regardless of prior episode of zoster

Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications)

No recommendation

These schedules indicate the recommended age groups and medical indications for which administration of currently licensed vaccines is commonly recommended for adults ages 19 years and older, as of February 1, 2015. For all vaccines being recommended on the Adult Immunization Schedule, a vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Licensed combination vaccines may be used whenever any components of the combination are indicated and when the vaccine's other components are not contraindicated. For detailed recommendations on all vaccines, including those used primarily for travelers or that are issued during the year, consult the manufacturers' package inserts and the complete statements from the Advisory Committee on Immunization Practices (www.cdc.gov/vaccines/hcp/acip-recs/index.html). Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.
<table>
<thead>
<tr>
<th>Diseases/Pathogens with Vaccines Generally Available in the U.S.</th>
</tr>
</thead>
</table>
Varicella Vaccine – Zoster (Zostavax)

Oxman et al, NEJM, June 2005

- Randomized trial 38,546 adults ≥ age 60
  - Excluded if history of zoster, immunocompromise
- Potency much greater (at least 14x) than vaccine to prevent primary varicella
- Zoster incidence reduced by > 50%; post herpetic neuralgia reduced by > 65%
- Injection site reactions common
Varicella Vaccine – Zoster (Zostavax) Newer Data

• 22,439 adults ages 50 – 59 randomized to zoster vaccine versus placebo
  – 30 cases in vaccine group versus 99 in placebo group
  – Vaccine efficacy 70%
  – More adverse events, mostly injection-site reactions, in the vaccine group

  Schmader et al, Clin Infect Dis 2012;54:922-8

• FDA approved Zostavax for persons 50 – 59 years of age in March 2011
Zostavax in HIV

- Phase II study sponsored by NIAID, presented at CROI 2012 (oral abstract #96)
- Randomized, blinded, placebo controlled trial of 2 doses of vaccine in HIV+ adults > 18, CD4>200, VL<75 copies
  - Stratified CD4 > 350 vs. CD4 200-349
- Based on VZV antibody response, vaccine was immunogenic
  - Antibody titer higher in higher CD4 count group
- Vaccine appeared safe; was associated with infection site reactions
Varicella Vaccine – Zoster (Zostavax)

- Recommended a single dose of zoster vaccine for adults age 60 and above, even if prior history of zoster
- Not necessary to ask about history of varicella or to do serologic testing (note VZV infects 98% of adult U.S. population per NHANES III data 2003)
- Contraindicated in many, but not all, immunocompromised persons (e.g. okay in HIV if clinically well and CD4 count > 200)
Varicella Vaccine – Zoster (Zostavax)

- Questions about cost effectiveness – multiple studies
  - Vaccine cost ~ $150 per dose
  - Societal costs $27,000 – 112,000 per QALY
- Vaccine is stored frozen
  - Once reconstituted, must be used within 30 minutes
- First vaccine covered by Medicare Part D – reimbursement was complicated
- May be given concurrently with Pneumovax - prior concerns decreased immunogenicity Zostavax
TENOFOVIR ALAFENAMIDE (TAF)

- TFV prodrug
- Up to 4x higher intracellular concentration in lymphoid cells
- Relative to TDF 300 mg, tenofovir alafenamide (TAF) 25 mg has 90% lower circulating plasma TFV, while maintaining high antiviral activity
- Phase III studies found TAF non-inferior to TDF
### TAF: Smaller Decreases in eGFR

#### Table:

<table>
<thead>
<tr>
<th>Events</th>
<th>E/C/F/TAF n=866</th>
<th>E/C/F/TDF n=867</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal adverse events leading to discontinuation</td>
<td>0</td>
<td>4 (0.5)*</td>
</tr>
<tr>
<td>Tubulopathy/Fanconi syndrome</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Sax P, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 143LB.
Switch to TAF: Improvement in proteinuria

Proteinuria and Albuminuria Change From Baseline at Week 48

<table>
<thead>
<tr>
<th>Baseline Grade</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 n=149†</td>
<td>95%</td>
</tr>
<tr>
<td>1 n=52</td>
<td>11%</td>
</tr>
<tr>
<td>2 n=22</td>
<td>27%</td>
</tr>
</tbody>
</table>

*Urine dipstick was used; 33% of patients (79/242) had proteinuria at baseline. †Patients with non-missing values at both baseline and Week 48.

Improved proteinuria = baseline Grade 0 → Grade 0, or baseline Grade 2 → Grade 1 or 0.
Worsened proteinuria = baseline Grade 0 → Grade 1, or baseline Grade 1 → Grade 2.

TAF vs. TDF: Spine and Hip BMD

<table>
<thead>
<tr>
<th></th>
<th>Spine</th>
<th>Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/C/F/TAF, n</td>
<td>845</td>
<td>836</td>
</tr>
<tr>
<td>E/C/F/TDF, n</td>
<td>850</td>
<td>850</td>
</tr>
</tbody>
</table>

Mean (SD) % Change from Baseline

<table>
<thead>
<tr>
<th>Week</th>
<th>E/C/F/TAF</th>
<th>E/C/F/TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>-1.30</td>
<td>-2.86</td>
</tr>
<tr>
<td>48</td>
<td>-1.30</td>
<td>-2.86</td>
</tr>
</tbody>
</table>

p < 0.001

Sax P, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 143LB.
What about Abacavir? NA-ACCORD: Recent Abacavir Use and Risk of MI

Study Design:
Retrospective analysis of pts in 7 clinical cohorts with recent ABC use from 1/1/1995 to 12/31/2010
ABC initiators (n = 1948) vs non-ABC initiators (n = 14,785):
“Full” study population: all ART users excluding persons on ABC at study entry
“Restricted” population: ART-naive persons who initiated ART in the cohort

Findings:
MI significantly associated with recent ABC use in restricted population and D:A:D replication
Association diminished after adjusting for additional CVD risk factors in multivariate analysis
Cochrane meta-analysis of pharmacologic interventions for smoking cessation: 2013

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Odds ratio (95% credible interval)</th>
<th>No. of studies (direct comparisons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRT vs Placebo</td>
<td>1.84 (1.71, 1.99)</td>
<td>119</td>
</tr>
<tr>
<td>Bupropion vs Placebo</td>
<td>1.82 (1.6, 2.06)</td>
<td>36</td>
</tr>
<tr>
<td>Varenicline vs Placebo</td>
<td>2.88 (2.4, 3.47)</td>
<td>15</td>
</tr>
<tr>
<td>Bupropion vs NRT</td>
<td>0.99 (0.86, 1.13)</td>
<td>9</td>
</tr>
<tr>
<td>Varenicline vs NRT</td>
<td>1.57 (1.29, 1.91)</td>
<td>0</td>
</tr>
<tr>
<td>Varenicline vs Bupropion</td>
<td>1.59 (1.29, 1.96)</td>
<td>3</td>
</tr>
</tbody>
</table>

**Posterior median odds**
Five A’s for tobacco cessation

Five "A's" for assessing for tobacco use and addressing smoking cessation

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask</td>
<td>Implement an officewide system that ensures that, for every patient at every clinic visit, tobacco-use status is queried and documented. Repeated assessment is not necessary in the case of the adult who has never used tobacco or has not used tobacco for many years, and for whom this information is clearly documented in the medical record.</td>
</tr>
<tr>
<td>Advise</td>
<td>Strongly urge all tobacco users to quit in a clear, strong, personalized manner. Advice should be:</td>
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<tr>
<td></td>
<td>- Clear - &quot;I think it is important for you to quit smoking now and I can help you.&quot; &quot;Cutting down while you are ill is not enough.”</td>
</tr>
<tr>
<td></td>
<td>- Strong - &quot;As your clinician, I need you to know that quitting smoking is the most important thing you can do to protect your health now and in the future. The clinic staff and I will help you.”</td>
</tr>
<tr>
<td></td>
<td>- Personalized - Tie tobacco use to current health/illness, and/or its social and economic costs, motivation level/readiness to quit, and/or the impact of tobacco use on children and others in the household.</td>
</tr>
<tr>
<td>Assess</td>
<td>Determine the patient’s willingness to quit smoking within the next 30 days:</td>
</tr>
<tr>
<td></td>
<td>- If the patient is willing to make a quit attempt at this time, provide assistance.</td>
</tr>
<tr>
<td></td>
<td>- If the patient will participate in an intensive treatment, deliver such a treatment or refer to an intensive intervention.</td>
</tr>
<tr>
<td></td>
<td>- If the patient clearly states he or she is unwilling to make a quit attempt at this time, provide a motivational intervention.</td>
</tr>
<tr>
<td></td>
<td>- If the patient is a member of a special population (eg, adolescent, pregnant smoker), provide additional information specific to that population.</td>
</tr>
<tr>
<td>Assist</td>
<td>Provide aid for the patient to quit. These actions are summarized in the accompanying table.</td>
</tr>
<tr>
<td>Arrange</td>
<td>Schedule follow-up contact, either in person or by telephone. Follow-up contact should occur soon after the quit date, preferably during the first week. A second follow-up contact is recommended within the first month. Schedule further follow-up contacts as indicated.</td>
</tr>
<tr>
<td></td>
<td>Congratulate success during each follow-up. If tobacco use has occurred, review circumstances and elicit recommitment to total abstinence. Remind the patient that a lapse can be used as a learning experience. Identify problems already encountered and anticipate challenges in the immediate future. Assess pharmacotherapy use and problems. Consider use or referral to more intensive treatment.</td>
</tr>
</tbody>
</table>

HIV Infection and BMD

- **Low BMD** demonstrated in many cohorts of untreated HIV infected pts
  - Prevalence of osteoporosis (by BMD) ~15%
  - ~3.7-fold increased vs age-matched controls
  - Associated risks: lower BMI, low CD4 counts, nutritional compromise, opiate use
  - “Traditional” risk factors: smoking, alcohol, glucocorticoid use, low Ca and vitamin D intakes, hypogonadism
  - HIV specific factors: chronic inflammation, HIV drugs, HIV/HCV co-infection

McComsey GA et al, CID, 2010; Rothman MS, Bessesen MT, Curr Osteo Rep, 2012; Maffezoni F et al, Eur Endo, 2014
Rates of bone fracture in HIV Outpatient Study (HOPS)

Fracture rates 1.98-3.69 times higher than in the general population.

Young et al, CID, 2011
Fracture Prevalence in HIV-Infected Patients (N=8,525) vs Non-Infected Controls (N=2.2 million): Partners Health Care System (retrospective)

Triant et al, JCEM, 2008
ART and BMD

• BMD declines (mass lost) w/institution of ART
  – Essentially all regimens, some more than others
  – Rates of loss 1.3 - 4% BMD in yr 1 & ongoing; 2-6%/2 yrs
  – Largest fall in first 6-12 mos
  – First 2 yrs of ART – likened to peri-menopause
  – Tenofovir (disoproxil fumarate) strongly associated with an acute decrease in BMD compared to abacavir
    • TAF associated with less significant decline

McComsey GA et al, CID, 2010; Rothman MS, Bessesen MT, Curr Osteo Rep, 2012; Young B et al, CID 2011, Sax et al JAIDS 2014
Rates of bone fracture in HIV Outpatient Study (HOPS)

Figure 1: Hip BMD T-score distribution by incident fracture (N=1,008)

Low BMD and age associated with significantly increased risk of developing fracture

Battalora et al, CROI 2014
USPSTF: Osteoporosis Screening

- **WOMEN:** screen if age 65 or older; all racial & ethnic groups; NO upper limit of age
- **“Younger women** whose fracture risk is = to > than that of a 65 yo white woman who has NO additional risk factors”
- **MEN:** insufficient evidence to recommend BMD screening for “men without previous known fractures or secondary causes of osteoporosis”
  - Does not include any discussion of HIV or mention specific 2° causes

*USPSTF; Jan 2011*
HIV Bone Guidelines:
DXA for postmenopausal women and men age ≥ 50

Secondary causes:
- Hypogonadism
- ETOH
- Tobacco
- PPIs
- Glucocorticoids

McComsey et al CID 2010
Aberg et al CID 2013
ACTHIV 2015: A State-of-the-Science Conference for Frontline Health Professionals

Activity Code SM737