CME Satellite Symposium

SURVIVING HIV
Addressing The Needs of Older Patients

Jointly Sponsored by The Annenberg Center for Health Sciences at Eisenhower and ViralEd, LLC in collaboration with the Postgraduate Institute for Medicine

Supported by an unrestricted educational grant by Merck & Co.
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DISCLAIMER
Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient’s conditions and possible contraindications on dangers in use, review of any applicable manufacturer’s product information, and comparison with recommendations of other authorities.

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AGENDA
Welcome and Opening Comments
Epidemiology of HIV/AIDS in 2010 (John Bartlett, MD)
ARV Therapy Considerations in an Aging Population (Calvin Cohen, MD)
Cardiovascular and Lipid Disease Risks and Prevention (Jorge Plutzky, MD)
Assessing and Managing Renal Disease (Jonathan Winston, MD)
Neurocognitive Disorders in HIV/AIDS (Glenn Treisman, MD)
Bone Disease and HIV/AIDS (Todd Brown, MD, PhD)
Patient Screening and Monitoring of an Aging Population (Trevor Hawkins, MD)
Patient Cases and Panel Discussion (Patient Presenters and Clinical Panel)
Closing Comments

Program Note: Presentations will last approximately 10 minutes with case presentations, panel discussion and audience participation throughout the entire program

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Orlando, Florida

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George Washington School of Medicine,
Washington, DC

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London, United Kingdom

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Los Angeles, California

Mauro Schechter, MD
Federal University of Rio de Janeiro,
Rio de Janeiro, Brazil
TARGET AUDIENCE
This activity has been designed to meet the educational needs of physicians involved in the management of patients with HIV infection.

COURSE DESCRIPTION
The success of antiretroviral therapy has allowed many HIV-positive patients to live a relatively normal lifespan. As a result, over the past decade, the percentage of older HIV-positive patients has been steadily increasing. In 2007, HIV-positive persons at least 50 years of age accounted for 24% of persons living with HIV/AIDS, 29% of persons living with AIDS, and 35% of all deaths of persons with AIDS. The aging HIV-positive patient has an increased risk for and rate of new and complex treatment issues and comorbidities.

This case-based satellite symposium will increase a health care provider’s ability to provide the health care needed by an aging HIV-positive patient population that is expected to have a normal lifespan. This program will deliver education regarding how to: appropriately screen and monitor for HIV-related conditions and non-AIDS-related comorbidities; prevent or mitigate conditions - including bone, renal, neurocognitive and cardiovascular disease - associated with increased morbidity and mortality; start ARV therapy and tailor it to the needs of the patient; and avoid and manage adverse drug-drug interactions.

This program is certified for CME credit for US physicians by the Annenberg Center for Health Sciences at Eisenhower.

LEARNING OBJECTIVES
Upon completion of the program, participants should be able to:
- Outline factors that play a role in ARV therapy success in older HIV-positive patients;
- Identify the important HIV/AIDS-related conditions and comorbidities that may affect older HIV-positive patients and increase their risk for morbidity and mortality;
- Evaluate how to effectively screen and monitor the older HIV-positive patient for HIV-related conditions and non-AIDS-related comorbidities;
- Outline how to clinically manage important, potential drug-drug interactions in older HIV-positive patients.

ACCREDITATION STATEMENT
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The Annenberg Center for Health Sciences at Eisenhower (Annenberg Center) and ViralEd, LLC. The Annenberg Center is accredited by the ACCME to provide continuing medical education for physicians.

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- Speakers Bureau: Gilead; Bristol-Myers Squibb; GlaxoSmithKline; Tibotec

Graeme Moyle, MD:
- Consulting Fees: Gilead; Bristol-Myers Squibb; Merck & Co.; ViV Healthcare; GlaxoSmithKline; Pfizer; Theratechnologies
- Speakers Bureau: Boehringer Ingelheim; Gilead; Bristol-Myers Squibb; Merck; ViV Healthcare; GlaxoSmithKline; Pfizer; Theratechnologies; Tibotec

Jurgen Rockstroh, MD:
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- Consulting Fees: Merck & Co.; Gilead; Boehringer Ingelheim; Bristol-Myers Squibb; GlaxoSmithKline; Tibotec; Pfizer
- Speakers Bureau: Merck & Co.; Gilead; Boehringer Ingelheim; Bristol-Myers Squibb; GlaxoSmithKline; Tibotec; Pfizer

Mauro Schechter, MD:
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- Consulting Fees: Bristol-Myers Squibb; Pfizer; Abbott

Francine: Nothing to Disclose

Clive: Nothing to Disclose

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Epidemiology of HIV/AIDS in 2010

John Bartlett, MD
Johns Hopkins University
School of Medicine

HIV Epidemiology: US
- Estimated new cases: 56,000/year and unchanged since 1990
- Population change by race and poverty
- Aging is major issue
- Older by chronology
- Even older by physiology

Estimates Rates of New HIV Infections by Race/Ethnicity, 2006

Epidemiology of HIV/AIDS in 2010

HIV Prevalence Rate by Income

HIV Prevalence Rate by Country
Surviving HIV: Addressing The Needs of Older Patients

Epidemiology of HIV/AIDS in 2010

John Bartlett, MD

HIV: Age at Diagnosis 2008

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Number</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;14</td>
<td>213</td>
<td>0.5*</td>
</tr>
<tr>
<td>15-19</td>
<td>1,870</td>
<td>12.6</td>
</tr>
<tr>
<td>20-29</td>
<td>9,099</td>
<td>37.5</td>
</tr>
<tr>
<td>30-39</td>
<td>10,514</td>
<td>37.9</td>
</tr>
<tr>
<td>40-49</td>
<td>10,811</td>
<td>35.6</td>
</tr>
<tr>
<td>50-59</td>
<td>5,137</td>
<td>18.1</td>
</tr>
<tr>
<td>&gt;60</td>
<td>1,051</td>
<td>30.0</td>
</tr>
</tbody>
</table>

* Estimated / 100,000

Risk of AIDS or Death Based on Age (Risk Calculator)

<table>
<thead>
<tr>
<th>CD4</th>
<th>Age 16-29 yrs</th>
<th>Age &gt;50 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>23%</td>
<td>35%</td>
</tr>
<tr>
<td>50-99</td>
<td>18%</td>
<td>29%</td>
</tr>
<tr>
<td>100-199</td>
<td>13%</td>
<td>21%</td>
</tr>
<tr>
<td>200-350</td>
<td>8%</td>
<td>13%</td>
</tr>
<tr>
<td>&gt;350</td>
<td>7%</td>
<td>11%</td>
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</tbody>
</table>

Impact of HIV and Aging on Immune Response

<table>
<thead>
<tr>
<th>HIV</th>
<th>Aging</th>
</tr>
</thead>
<tbody>
<tr>
<td>B cells:</td>
<td></td>
</tr>
<tr>
<td>Repertoire</td>
<td></td>
</tr>
<tr>
<td>Primary response</td>
<td></td>
</tr>
<tr>
<td>Resting proliferation</td>
<td></td>
</tr>
<tr>
<td>T cells (CD4):</td>
<td></td>
</tr>
<tr>
<td>Naive (number)</td>
<td></td>
</tr>
<tr>
<td>Activation</td>
<td></td>
</tr>
<tr>
<td>CD8 cells:</td>
<td></td>
</tr>
<tr>
<td>Activation</td>
<td></td>
</tr>
<tr>
<td>Senescence phenotype*</td>
<td></td>
</tr>
</tbody>
</table>

* CD8+ short telomeres, dC dT, cytokines

Impact of HIV and Aging on Immune Response (cont’d)

- Left: Russell Steinke. Age: 56 / HIV: 23 years / Suffered from memory loss, nerve damage in feet, lipodystrophy, fatigue.
Epidemiology of HIV/AIDS in 2010

**HIV Infection and Aging Independently Affect Brain Function by Functional MRI**

- **Method**
  - MRI in age matched persons with HIV (n=25) and without HIV (n=36)
  - Goal = changes in visual cortex due to impact of aging
  - HIV patients - med CD4 486, 60% HAART
- **Results**
  - HIV infection added 21 years to brain age

Santos BM, JID 2010;201:1330

**Coronary Aging in HIV-Infected Patients**

- **Method**: Cross-sectional study, 400 patients (mean age 48) had cardiac CT for coronary artery calcium (CAC)
- **Results**: 162 patients (40%) had increased vascular age with average of 15 years over chronological age


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**Conclusion: HIV, Aging, and Epidemiology**

- **HIV-infected patients**: Getting older chronologically and physiologically
- **Consequences**: CVD, malignancy, frailty, neurocognitive loss
- **Cause**: Immune activation?
- **Treatment**: HAART plus ____

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**NOTES**
# ARV Therapy Considerations in an Aging Population

**Calvin Cohen, MD**

**Harvard Medical School**

## Life Expectancy of HIV-Positive Patients

- Comparison of life expectancy: Athena cohort to general population (n=4174)
- Associations with risk of death:
  - Age
  - Country of birth
  - Stage B symptoms
  - Expected life years remaining at age 25:
    - 83.1 (44.9-95.5) for general population
    - 72.7 for asymptomatic HIV+ patients

## IAS-USA 2010: Guidelines for When to Start ARV Therapy

<table>
<thead>
<tr>
<th>Measure</th>
<th>ARV recommended regardless of CD4 cell count</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 cell count ≤500 cells/mm³</td>
<td>ARV recommended</td>
</tr>
<tr>
<td>CD4 cell count &gt;500 cells/mm³</td>
<td>ARV should be considered¹</td>
</tr>
</tbody>
</table>

## 2009 DHHS Guidelines: Recommendations for Initiation of ART in Naïve Patients

**Clinical Category** | **CD4 Cell Count (cells/mm³)** | **2009 DHHS Guidelines** | **Strength-Quality** |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS-defining illness</td>
<td>Any value</td>
<td>Treat</td>
<td>A-4</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&gt;200</td>
<td>Treat</td>
<td>2B</td>
</tr>
</tbody>
</table>

## 2009 DHHS Guidelines: Regimens for Treatment-Naïve Patients

**Preferred Regimens**

- LPV/r + ATV (or/and) + TDF/FTC
  - [Protease Inhibitor/Integrase Inhibitor/Nucleoside Reverse Transcriptase Inhibitor] (PI/INN/NNRTI)

**Alternative Regimens**

- ETV + ATV (or/and) + TDF/FTC
- ETR (or/and) + DRV/c (or/and) + TDF/FTC
- ATV/c (or/and) + TDF/FTC
- LPV/r (or/and) + TDF/FTC
- PI (or/and) + NRTI

**Acceptable Regimens**

- ETV + ATV (or/and) + TDF/FTC
- ETR (or/and) + DRV/c (or/and) + TDF/FTC
- ATV/c (or/and) + TDF/FTC
- LPV/r (or/and) + TDF/FTC

**Insufficient Data**

- ETR + TDF/FTC
- ATV/c + TDF/FTC
- ATV/c (or/and) + TDF/FTC

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¹ Data from cohort analysis.
**Summary**

- Current recommendations suggest treating sooner in those who are "older" given higher risk of HIV-related events.
- Specific regimens are not influenced by age.
- While some outcomes are improved by age, some are hampered.
Surviving HIV: Addressing The Needs of Older Patients

CV and Lipid Disease Risks and Prevention

Jorge Plutzky, MD

Cardiovascular and Lipid Disease Risks and Prevention

Jorge Plutzky, MD
Director, Vascular Disease Prevention Program
Cardiovascular Division
Brigham and Women's Hospital
Boston, Massachusetts

Atherosclerosis, CVD

Risk of MI in Patients Presenting at Least Twice to Either of Two Boston Hospitals By HIV Status

ART-associated Metabolic Abnormalities are Not the Only Risk Factors for Increased CVD

- Antiretroviral therapy, especially protease inhibitors, main driver of CVD in HIV
- SMART: 5972 HIV patients
  - Randomized to continuous ART vs. intermittent ART guided by CD4 count (start when <250 and stopped when >350)
  - Hypothesis: ART sparing strategy superior
  - Study terminated early due to increased events in ART sparing group.
  - Role of unsuppressed viral infection and inflammation in HIV atherosclerosis and CVD

Studies of CVD in HIV

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N (HIV)</th>
<th>Primary Disease</th>
<th>Control Group</th>
<th>Perpective (Study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAI, NEM 011</td>
<td>31 HIV Cohorts</td>
<td>2946</td>
<td>PI Therapy vs Years</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Narayanan et al, AIDS 2003</td>
<td>French Hosp.</td>
<td>34276</td>
<td>PI Therapy vs Years</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Baracos et al, AIDS 2003</td>
<td>VA System</td>
<td>26466</td>
<td>PI Therapy vs Years</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Currer et al, J AIDS 2003</td>
<td>CA Medicaid</td>
<td>20513</td>
<td>CHD - n = 2544 vs. Control</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Aran et al, J AIDS 2003</td>
<td>4139</td>
<td>CHD and ART vs. No ART vs Control</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Charlton et al, J CCM 2007</td>
<td>12 HIV Cohorts</td>
<td>1851</td>
<td>ART vs. No ART vs Control</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

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Primary and Major Secondary End Points

<table>
<thead>
<tr>
<th>Event</th>
<th>No. of Patients with Events</th>
<th>Hazard ratio (CCS vs. YV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opportunistic disease or death</td>
<td>167</td>
<td></td>
</tr>
<tr>
<td>Major CV, hepatic or renal disease</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>Fatal or non-fatal CV disease</td>
<td>79</td>
<td></td>
</tr>
</tbody>
</table>

Inflammatory markers (IL-6, D-dimer) predictors of CV events, even at higher CD4 counts.

HIV, Inflammation as CV drivers?

---

HIV Infection: An Independent CVD risk factor

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Estimated effect (per unit)</th>
<th>Internal carotid</th>
<th>Common carotid</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td>0.18**</td>
<td>0.033**</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.13***</td>
<td>0.051**</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.17***</td>
<td>0.022**</td>
<td></td>
</tr>
<tr>
<td>Past smoker</td>
<td>0.08**</td>
<td>0.022**</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.12***</td>
<td>0.024***</td>
<td></td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>0.16***</td>
<td>0.037***</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (per 10 mmHg)</td>
<td>0.05***</td>
<td>0.021***</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (per 10 mmHg)</td>
<td>0.06***</td>
<td>0.021***</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (per 10 mg/dL)</td>
<td>0.09***</td>
<td>0.009***</td>
<td></td>
</tr>
<tr>
<td>HDL (per 10 mg/dL)</td>
<td>-0.029***</td>
<td>-0.011***</td>
<td></td>
</tr>
</tbody>
</table>

---

Factors Associated with Coronary Segments with Plaque in HTLV

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Spearman Rho</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>0.40</td>
<td>0.0004</td>
</tr>
<tr>
<td>Framingham Risk Score</td>
<td>0.43</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>0.35</td>
<td>0.002</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>0.32</td>
<td>0.005</td>
</tr>
<tr>
<td>Duration since HIV diagnosis</td>
<td>0.27</td>
<td>0.0006</td>
</tr>
<tr>
<td>Duration of PL use</td>
<td>0.27</td>
<td>0.04</td>
</tr>
<tr>
<td>CD4+/CD8+ ratio</td>
<td>-0.25</td>
<td>0.03</td>
</tr>
<tr>
<td>MCP-1</td>
<td>0.23</td>
<td>0.047</td>
</tr>
<tr>
<td>Cytomegalovirus IgG Titer</td>
<td>0.25</td>
<td>0.03</td>
</tr>
</tbody>
</table>

---

Subclinical Coronary Disease by Coronary CT Angiography

- HIV pts and controls: No CVD sx or hx.
- Similar Framingham risk.
- Smoking rates similar.

---

HIV Related Issues That May Promote CVD

- Inflammation
- Adherence
- Behavior
- HIV Infection
- ART
- Other CVD Risk Factors
- HIV Infection + ART
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CV and Lipid Disease Risks and Prevention

Jorge Plutzky, MD

Dyslipidemia in HIV Infection

Pre-HAART
- Hypertriglyceridemia
- Low HDL
- Low LDL

PI-based HAART
- Hypertriglyceridemia worsens
- HDL increases, then decreases
- LDL increases

Effect of Exposure to PI and NNRTI – before and after adjusting for Lipids

Relative Rate of MI (95% CI)

Prevalence of DM in MACS Cohort

Prevalence Ratio 2.2
(CI 1.1-4.4)

Prevalence Ratio 4.0
(CI 3.0-7.1)

Potential Mechanisms of Insulin Resistance and Diabetes in HIV

- Fat redistribution (lipodystrophy, VAT), altered adipokine levels
- PI and NRTIs promote DM (Swiss HIV Cohort Study, Lobergeder et al. CID 2007)
- PIs reduce glucose transporter (Glut 4)
- Impaired mitochondrial function
- Increased inflammation, inflammatory cytokines
- Hep C, HIV co-infection associated with higher T2D risk (Veterans Aging Cohort Study, Butt et al. AIDS 2000)

Thank you

CVD in HIV
Surviving HIV: Addressing the Needs of Older Patients

Assessing and Managing Renal Disease
Jonathan Winston, MD
Mount Sinai School of Medicine

Kidney Disease and Aging

- Factors contributing to the increased burden of kidney disease with aging:
  - Some misclassification due to physiologic decline in GFR
  - Increased burden of hypertension, diabetes, CHF, CAD, ESRD, HIV, and cancer
  - Improved overall survival following stroke, ARF, cancer diagnosis, etc.


Challenges in Studying Kidney Disease in HIV
- The syndrome of CKD conforms to a precise formula but the CAUSE of CKD is ascertained by the clinical history and therefore subject to interpretation
- The impact of kidney disease on outcomes are quantified from observational studies, not RCT
- Cause and effect relationships are often open to interpretation

Kidney Disease and Aging in HIV
- Renal events are rare in patients initiating ARV treatment
  - First Study
    - Median age: 30-38 y
    - Renal events 1% in Blacks, 0.3% in whites
- VACS: kidney disease increases with age
  - Overall prevalence of 3% in VACS cohort compared to 1% in age-matched controls
  - Prevalence of 1% in patients <40 years
  - 3% age 40-49
  - 4% age 50-59
  - 6% age >60

Spectrum of Kidney Disease in HIV
- HIV-associated nephropathy, HIV-associated immune complex disease, thrombotic microangiopathies are often discussed, but their relative contribution to kidney disease burden appears to be decreasing
- Hypertension, diabetes, and atherosclerotic vascular disease appear to be much more common
Surviving HIV
Addressing The Needs of Older Patients

Assessing and Managing Renal Disease

Jonathan Winston, MD

VA Cohort: Association Between Decreased GFR, Albuminuria, and CVD Risk in HIV+ Patients

- 17,264 HIV+ persons receiving care in the VA for:
  - Incident CVD defined as coronary, cerebrovascular, or congestive heart failure
  - Incident heart failure
- 7% of patients had reduced kidney function (eGFR <60 mL/min per 1.73 m²) at study entry

Assessing and Managing Renal Disease

Jonathan Winston, MD

Antiretroviral Therapy and CKD

- Tenovir is associated with a decrease in GFR and renal tubule dysfunction
- PI's are associated with crystalluria and interstitial disease
- Tenovir is recommended as part of a preferred regimen in DHHS and IAS guidelines
- IAS, DHHS, and IDSA guidelines re: tenovir use and kidney disease are clear and rational
- Avoid tenovir when GFR is below 60 mL/min - CQI ratio in elderly patients
- There are few guidelines that directly address tenovir use in patients with normal kidney function but who have risk factors for CKD, particularly older, drug experienced individuals

Kidney Function and Tenofovir

- Early identification of kidney disease by using eGFR equations and screening for proteinuria with a routine urinalysis
  - Diagnose the underlying cause of kidney disease
  - Screen for microalbuminuria in diabetes because of the high risk for subsequently developing kidney disease
  - Screen for microalbuminuria in patients with hypertension or dyslipidemia because of their high risk for CV disease
- It is unclear whether the prevalence of microalbuminuria is significant in low-risk patients (no hypertension, DM, or dyslipidemia) and whether routine screening for microalbuminuria in these patients is worthwhile
- Targeted cardiovascular risk factor modification
  - Liberal use of ACE inhibitors or ARBs (but not diuretics)
  - Switch to regimens that are more lipid and glycemic friendly, particularly in patients with microalbuminuria

Acute Renal Failure

- AKI is a marker of underlying vascular disease, not necessarily an independent mortality risk
- Predictors of AKI:
  - Diabetes, CKD, sepsis, CRP, hemoglobin, creatinine, calcium, uric acid, use of diuretics, mechanical ventilation
- 3,769 adults with AKI requiring dialysis from Canadian Institute for Health Information (Discharge Abstract) database
- All patients had recovered renal function to discontinue dialysis and survived for >30 days after discharge
- Outcomes compared to controls matched for age and co-morbidity
- Cumulative risk for ESRD requiring dialysis was greater in patients who had AKI compared to controls: >5% compared to <3% in matched controls (20% incidence of ESRD after 10 yrs)
- There was no difference in ALL-CAUSE MORTALITY >10,000 person years between AKI patients and controls (40% of patients had died by 10 years)
Neurocognitive Disorders in HIV/AIDS

Neurocognitive Disorders in HIV/AIDS
Glenn Treisman, MD
Johns Hopkins School of Medicine

Treatment of Depression Improves Survival

Interactions of Age and Psychiatric Conditions

The Four Perspectives
McHugh and Slayney

- Disease
- Temperament
- Behavior
- Life Story
Neurocognitive Disorders in HIV/AIDS

Primary Symptoms of Depression

- Mood
- Vital sense
- Self attitude
- Anhedonia

Factors Associated with Depression

- CNS inflammation
- Auto-immune disease
- Substance abuse
- Genetic vulnerability
- Subcortical damage
  - HIV and HEP-C
  - Ageing

The Triad Associated with Subcortical Dementia

- Dyskinesia
- Dementia
- Depression

Subcortical Pattern of Dementia

- Memory loss with selective impairment of retrieval
- Impaired manipulation of acquired knowledge
- Personality changes with apathy, inertia, and irritability (personality deterioration or coarsening)
- General slowing of thought processes

AIDS Dementia

- Useful screens are directed at psycho-motor speed
- Grooved pegboard
- Symbol-digit substitution
- Trail-making (Part-B)
Neurocognitive Disorders in HIV/AIDS

Summary: Things We Should Do
1. Diagnose and treat depression
2. Screen for HIV cognitive impairment
3. Induce treatment for addiction
4. Induce treatment for personality disorder
5. Guidelines are aimed at the average trials subject, not at your patient: always individualize treatment

What We Need to Know and Think About
- How important is CNS penetration? (LP?)
- How do we evaluate efavirenz induced CNS effects?
- How do we prioritize CNS issues, resilience to resistance, cardiovascular risk, renal risk, hepatic risk and Hep C treatment?
- When do we start treatment with patients with high risk for poor adherence?

NOTES
Surviving HIV
Addressing The Needs of Older Patients

Bone Disease and HIV/AIDS
Todd Brown, MD, PhD
Johns Hopkins School of Medicine

Prevalence of Osteoporosis in HIV-infected Patients vs HIV-uninfected Controls: a Meta-analysis

Pathophysiology and Risk Factors
- Medication Factors
  - Protease inhibitors
  - tenofovir (TDF)


A5224s: Mean (95% CI) Percent Change in Hip and Spine BMD (ITT)
Surviving HIV Addressing The Needs of Older Patients

Patient Screening and Monitoring of an Aging Population

Trevor Hawkin, MD

University of New Mexico

HIV and Aging

1. Does HIV cause aging directly or is it associated with the diseases of aging or both?
   - Evidence very strong for association with diseases
   - In vitro data suggest a direct effect on aging

2. How can we screen/prevent both effects?

3. How does this differ from our current screening algorithms for HIV negative patients as they age?

4. Be forewarned, there are way more questions than answers!

HIV and Aging - Screening and Prevention

First The Direct Effects of HIV Replication

2009 DHHS Guidelines: T-cell Activation and Inflammation

- Early untreated HIV infection associated with sustained high-level inflammation and T-cell activation that are associated with disease progression
- ART results in a rapid, but often incomplete, decrease in most markers of HIV-associated immune activation
  - Persistent inflammation, as represented by levels of IL-6, may be associated with risk of death
- These observations support earlier use of ART:
  - Treatment decreases the level of inflammation and T-cell activation; and
  - Degree of residual inflammation and/or T-cell dysfunction during ART is higher in patients with lower CD4 cell nadirs and/or earlier treatment may result in less residual immunologic perturbations

CD8+ T-cell Activation (and Other Markers of Inflammation) Decline During HAART, but Remains Abnormal

The Cascade of Events Due to Chronic Immune Activation and Inflammation

- Low-Level Viral Replication
- Secretion of Proinflammatory Cytokines
- Chronic Inflammation
- Immune Senescence
- Osteoporosis, Atherosclerosis, Neurocognitive Degeneration, Frailty, Metabolic Syndrome, etc.

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Surviving HIV: Addressing the Needs of Older Patients

Patient Screening and Monitoring of an Aging Population

Trevor Hawkins, MD

Despite Durable Treatment-mediated Viral Suppression, Endotoxin (LPS) Remains High

Potential Strategies to Prevent Immune Activation and Inflammation

- To cate, efforts to suppress low level viremia by intensifying already suppressive regimes, e.g., with RAL or MVC have failed.
- Supports thesis that this viremia is from the latent pool.
- Efforts to block CCR5 receptors to decrease immune activation (as in Sooty Mangabey monkeys) have met with very limited success.
- Will CCR2 blockade be helpful? CCR2 remains associated with and studied in atherosclerotic and metabolic syndrome/insulin resistance.

Potential Strategies to Prevent Immune Activation and Inflammation (cont’d)

- Can we activate the latent pool?
  - Histone deacetylase inhibitors
  - Kinase agonists
  - Prostratin

- Can we block downstream inflammatory effects?
  - CCR5 inhibitors
  - STAT3/ASA
  - TLR 7/8 Blockers e.g., chloroquine

Liver Disease: One of the Leading Causes of Death in HIV-infected Persons

Factors Predicting Osteoporotic Fracture in HIV Patients

<table>
<thead>
<tr>
<th>Factors</th>
<th>Hazard Ratio (95% Confidence Interval; P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV Co-Infection</td>
<td>1.27 (1.11 – 1.44; P = 0.0001)</td>
</tr>
<tr>
<td>CD4 (cells/μL)</td>
<td>1.34 (1.03 – 1.74; P = 0.041)</td>
</tr>
<tr>
<td>White Race</td>
<td>1.64 (1.41 – 1.90; P = 0.0001)</td>
</tr>
<tr>
<td>Age (per 10 year increase)</td>
<td>1.49 (1.40 – 1.59; P = 0.0001)</td>
</tr>
<tr>
<td>ART Use</td>
<td>0.57 (0.43 – 0.77; P = 0.0001)</td>
</tr>
<tr>
<td>Tobacco Use</td>
<td>1.30 (1.14 – 1.48; P = 0.0001)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.18 (1.02 – 1.37; P = 0.01)</td>
</tr>
<tr>
<td>BMI &lt;20</td>
<td>1.54 (1.29 – 1.82; P = 0.0001)</td>
</tr>
</tbody>
</table>
**SURVIVING HIV: ADDRESSING THE NEEDS OF OLDER PATIENTS**

**Patient Screening and Monitoring of an Aging Population**

**CME Satellite Symposium**

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**SVR is Sustained and Reduces Risk for Liver-Related Morbidity and Mortality**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>TLV + Peg</th>
<th>TLV + Peg/GR</th>
<th>TLV + Peg/GR</th>
<th>Peg/GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>12 wks</td>
<td>12 + 12 wks</td>
<td>12 + 36 wks</td>
<td>24 wks</td>
</tr>
<tr>
<td>SVR</td>
<td>35 - 62%</td>
<td>61 - 68%</td>
<td>67%</td>
<td>36%</td>
</tr>
</tbody>
</table>

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**Telaprevir: HCV genotype 1 with No Prior Treatment**

**Boceprevir: HCV genotype 1 with No Prior Treatment**

**Look to the Long-Term, in Money and in HIV**

**The Burden of Cancer Among HIV-Infected Persons in the US Population**
Surviving HIV: Addressing the Needs of Older Patients

Patient Screening and Monitoring of an Aging Population

Trevor Hawkins, MD

Cancers Incidence in Ponce Clinic Patients Compared to Atlanta Metro Area

<table>
<thead>
<tr>
<th>Cancers</th>
<th>N</th>
<th>SIR*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal/rectal SCC</td>
<td>24</td>
<td>67.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hodgkin's Lymphoma</td>
<td>16</td>
<td>15.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepatocellular Cancer</td>
<td>10</td>
<td>9.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Head and Neck Cancer SCC</td>
<td>22</td>
<td>9.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>40</td>
<td>4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>11</td>
<td>1.6</td>
<td>0.18</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>18</td>
<td>0.5</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Average Age at NADC Diagnosis HIV Clinic (IDP) Versus Metro Atlanta Population

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Age at cancer IDP</th>
<th>Age at cancer Atlanta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal/Rectal SCC</td>
<td>40.9</td>
<td>35.1</td>
</tr>
<tr>
<td>Hodgkin's Lymphoma</td>
<td>39.7</td>
<td>41.7</td>
</tr>
<tr>
<td>Liver</td>
<td>43.7</td>
<td>59.5</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>50.7</td>
<td>60.0</td>
</tr>
<tr>
<td>Lung</td>
<td>51.6</td>
<td>60.3</td>
</tr>
<tr>
<td>Breast</td>
<td>44.9</td>
<td>57.7</td>
</tr>
<tr>
<td>Prostate</td>
<td>53.4</td>
<td>64.4</td>
</tr>
</tbody>
</table>

Functional Issues with Aging and HIV

- Frailty phenotype (presence of >3 of the following)
  - Exhaustion, slowed walking speed, low activity level, weakness, and weight loss
  - Associated with poorer health outcomes
- MACS
  - A 65-year-old HIV-infected person has similar frailty as a 55-year-old HIV-negative person
- Proposed mechanisms:
  - Mitochondrial dysfunction and increased number of free radicals and cytokines activate inflammatory pathways, ultimately leading to frailty

Psychosocial Issues

- Disclosure
- Isolation
- Lack of support
- Financial/assets/poverty
- End of life suffering/poor pain management
- Suicide

HIV Treatment May Be Complicated by Polypharmacy

- Overlapping toxicities
- Drug-drug interactions
  - Increase or decrease in drug plasma levels
  - Inadequate levels of ARVs may lead to incomplete viral suppression and development of resistance
  - ART-induced organ toxicities may exacerbate pre-existing age-related conditions
- Close monitoring is required to detect any emerging problems
Drugs Used by Older Patients that May Interact with ARVs

- HMG-CoA reductase inhibitors (statins)
  - Simvastatin/lovastatin
- Selected antihypertensive agents (eg, amiodarone)
- Medications that inhibit gastric acidity
- Anticonvulsants
- St. John’s Wort
- Midazolam
- Warfarin
- Selective serotonin reuptake inhibitors
- Erectile dysfunction agents
- Methadone
- Methamphetamine
- Calcium channel blockers
  - Amlodipine, nifedipine, verapamil
- Carvedilol

Lipid-Lowering Agents and PIs: Drug-Drug Interactions

- Fibrates
- Resins
- Pravastatin
- Ezetimibe
- Fish oil
- Statin + fibrates
- Amlodipine
- Rosuvastatin
- Niacin
- Lovastatin

Screening in HIV Patients

1. Start ART earlier because older patients have slower CD4 recovery and more comorbidities
   - Any CD4 count?
2. Monitor and aggressively manage CVD risk factors
   - Smoking cessation, moderate use, BP, lipids, DS and insulin resistance, weight gain, exercise, diet, stress, depression
   - Should we measure hA1c, D-dimer, fibrinogen levels?
   - Should HIV be a part of the Framingham equation?
   - Should some drugs, e.g., IDV or ABC, be part of the equation as suggested by D.A.D.?

Screening in HIV Patients (cont’d)

3. DXA scans and vitamin D levels
   - Should all patients with HIV over 40, over 50, have a dx? How many years? Most favor >50 years
   - What if there is at least 1 additional risk factor such as smoking, low BMI, white race, hypogonadism, steroid use, HCV, etc? Many favor DXA at any age in this group
   - What is the optimal vitamin D level? >20 ng/mL? >60 ng/mL? Most docs are replacing at <30 ng/mL and rising it.

4. Monitor Serum Creatinine/GFR
   - UA dip for protein and glucose/spot urine P/C ratio
   - Are these sufficient?

Screening in HIV Patients (cont’d)

5. Neurocognitive mini screen/Depression scores
   - Memory/Albert/diagnostic/psychometric speed/astroball
   - Need to eliminate the stigma of the dx of HIV in the elderly
   - Work, retirement, remaining engaged with family and friends

6. Cancer Screening
   - All usual including vaginal PAP, breast exam, and mammography, colonoscopy, ERC + PSA
   - Anal PAP + HRA should be part of SOC
   - Cancer screening in HIV infected patients should be considered at an earlier age than in the general population

Conclusions

- Toxicity from HAART is substantial and may be exacerbated in older patients
- Drug-drug interactions are common
- Unclear what the “ideal” HIV regimen is for older patients
- High rates of comorbidities in older HIV patients
- General routine health maintenance and screening is important
- Future research is essential for developing accurate treatment recommendations in older patients