HIV Complications Update

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Updated Disclosures

• Research Grant to UCLA from Theratechnologies
Long-Term Mortality in HIV-Infected Individuals 50 Years or Older: A Nationwide, Population-Based Cohort Study

Subset of Well-Controlled HIV
- No prior co-morbidities
- Viral load < 500
- Still had reduced survival Compared to matched pop controls

Chronic liver disease
Cognitive disorders
Non-AIDS cancers
Chronic renal disease
Osteoporosis
CVD
Frailty
Depression
Diabetes mellitus
COPD
Long Term Complications of Treated HIV Disease

• Epidemiology of Non AIDS Events
• Pathogenesis
• Interventions

True or False

I manage all aspects of care of primary care for the HIV positive patients in my practice?

A. True
B. False


Meta-analysis of 19 studies reporting deaths in cohorts on ART

Prevalence of Non-AIDS Deaths
53% high income settings
34 % developing country settings
18% Sub-Saharan African setting

Among Non-AIDS deaths, CV, Cancer, Liver disease were most common

Adapted from Farahani, M et. al Int J STD AIDS February 10, 2016 as doi:10.1177/0956462416632428
Future challenges for clinical care of an ageing population infected with HIV: a modelling study

- Modelling study projected HIV population in Netherlands
- By 2030
  - 28% of HIV-infected patients
  - 54% of HIV-infected patients will be on medications to treat NCDs

Evidence for Increased Risk CHD in HIV

- 2003 MediCal Claims data, excess risk highest in younger age groups
  (Currier J et al, JAIDS, 2003)

- 2007 Partners Cohort RR MI 1.75 in HIV+ compared to HIV−
  (Triant V et al. JCEM, 2007)

- 2013 VA 50% increased risk of AMI after adjustment for risk factors; also noted for women
  (Freiberg, M et al. JAMA IM, 2013; Womak 2014)

Trends in Mortality due to CVD in HIV: US 1999-2013

Trends in Mortality due to CVD in HIV: US 1999-2013


Non-Calcified Coronary Plaque more Common in HIV

- UCLA Autopsy Study:
  - Higher rate of >75% stenosis in HIV compared to control and unusual patterns of calcification in advanced HIV patients (in internal elastic lamina) (Micheletti, RG et al. Cardiovasc Pathol. 2009 Jan-Feb;18(1):26-36.)
  - Non-calcified plaque associated with immune activation in HIV
  - MACS Cohort (Post W, et al Am Heart J 2016)
    - HIV+ associated with non-calcified plaque score (p=0.03), along with HTN, DM, dyslipidemia

Cardiac Function

- Cardiac MRI Studies
  - High burden of myocardial fibrosis, cardiac steatosis among Asx HIV-infected individuals
  - Decreased systolic function in HIV compared to controls
  - Increased pericardial fat among HIV-infected individuals with lipa-accumulation

<table>
<thead>
<tr>
<th>Heart Failure Clinical Studies: HIV increases risk of HF</th>
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<tbody>
<tr>
<td>HIV+</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
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<tr>
<td>Heart Failure Preserved Ejection Fraction (EF&gt;40)</td>
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<tr>
<td>HIV+</td>
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<td>HIV</td>
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<tr>
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</table>
A single measurement of IL-6 or D-dimer predicts Serious Non-AIDS events (SNA)/mortality over next 10y

Biomarkers IL-6, d-Dimer and hs CRP for Clinical Events: SMART and ESPRIT

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>1st Quartile</th>
<th>2nd Quartile</th>
<th>4th/1st Quartile</th>
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<tbody>
<tr>
<td>Non-AIDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Malignancy</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Death</td>
<td></td>
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</table>

- IL-6 is a stronger predictor of CVD and malignancy than d-Dimer but its overall independent associations of CVD were stronger for non-AIDS related deaths and all cause deaths and similar for CVD and non-AIDS malignancy.

Adapted from Borges, AH, INSIGHT SMART AND ESPRIT Groups, JID 2016:214 (1 August)

Biomarkers

- Several studies demonstrate that biomarkers such as IL-6, sCD14 or the CD4/CD8 ratio may help identify those patients at increased risk for non-AIDS events.
- Prediction models for combinations of these markers are being tested currently.
- At present these are not ready for widespread clinical use. It is also not clear that they will identify patients you could not already recognize at being of high risk due to traditional risk factors.
- Stay tuned.

What Contributes to the Risk of Non AIDS Events in HIV?

- Host Genetics
- Lifestyle
- Virus/Immune System
- Antiretroviral Therapy (ART)
Contributions of ART to CVD

- The ‘toxicity’ of untreated HIV disease outweighs any excess risk of CVD associated with ART.
- Long duration of older protease inhibitors (indinavir, lopinavir/r) associated with increased MI risk in observational trials; however, no association between ART agents and CT angiographic evidence of plaque.
- Abacavir has been associated with increased relative risk of MI; most consistent findings among patients with other risk factors.
- What about other contemporary agents?

A5260: A Clinical Trial to Assess ART and Complications

- Phase III, prospective, multicenter randomized, open-label trial (Novelsg).
- ART-naive, HIV+ subjects ≥18 yr, VL ≥1000 c/mL.
- Randomized 1:1:1 to three NNRTI-sparing ARV regimens.
- Stratified by screening HIV-1 RNA level (≥ or <100,000 copies/ml), Framingham 10-year CHD risk score (<6% vs ≥6% risk), and A5260s participation.

Study Design

- Agelis Substudy (N=328)
  - No known CVD, diabetes mellitus, or use of lipid-lowering medications.
- Participants followed for 96 weeks after enrollment of last subject.
- At baseline and week 96:
  - DXA scan (limb fat, trunk fat, and lean mass).
  - CT abdomen (visceral and subcutaneous abdominal fat).
  - At baseline:
    - cotinine, adiponectin, IL6, hs-CRP, D-dimer, sCD14, sCD163.

How Does ART Impact Biomarkers?

ACTG S260s: ATV/r, RAL, DRV/r

- Examined fold change in biomarkers among participants who maintained viral suppression over 96 weeks.
- RAL associated with a persistent decline in IL-6 where as ATV/r and DRV/r were not.
- D-Dimer declined with ATV/r and DRV/r but not RAL.
- Measures of T cell activation declined in all groups, monocyte activation was inconsistent.
Plasma levels of oxidized HDL decrease whereas plasma levels of oxidized LDL increase with initiation of ART in ART naïve HIV infected persons with low cardiovascular risk

Kelesidis et al Antivir Ther. 2016 [in press]

Progression of Carotid Intima Medial Thickness and ART: Slower rate with ATv/r

CCA and bifurcation: significant CIMT progression within each arm (μm/year)
- Bilirubin levels > 0.6mg/dl at week 4 and 24 associated with slower rate of progression of IMT.
- Is atazanavir protective against CVD in HIV?

More on Atazanavir, Bilirubin and MI risk

- Cohort studies have evaluated this association
  - CNICS cohort: 22,689 people, 568 MI or ischemic stroke (Crane et al, 2014)
    - Higher bilirubin levels associated with lower risk of T1 MI and stroke, but also with higher risk for T2MI (those due to oxygen supply demand mismatch such as in sepsis)
  - VA study (LaFleur, J et al; 2016)
    - Lower risk of MI for those on ATv regimen (HR 0.66), no difference in stroke rates
- Atazanavir no longer considered a preferred agent due to higher risk of d/c due to bilirubin
- Might consider in a patient at high CVD risk
The Role of Adipose Tissue

“It’s an uncommonly dangerous thing to be left without any padding against the shafts of disease.”
—George Eliot, Middlemarch

Adipose Tissue

• Major endocrine organ closely associated with the immune system
  • Fat surrounds lymph nodes
  • Adipocytes are prominent in bone marrow and fat depots
  • CD4+ T cells in fat have activated memory phenotype
  • In obesity fat becomes pro-inflammatory with influx of CD8+ T cells that secrete IL-6 and TNF-alpha, these factors may stimulate HIV replication and or contribute to CVD, insulin resistance, diabetes and dyslipidemia
  • Two groups have reported on possible role of adipose tissue as a reservoir of HIV (Couturier AIDS 2015,29:667-674; Damouche, A. et al Plos Pathog. 11, e1005153)

Body Mass Index kg/m² Categories

<table>
<thead>
<tr>
<th>BMI Category</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5 - 24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25 - 29.9</td>
</tr>
<tr>
<td>Obese</td>
<td>30 - 40</td>
</tr>
<tr>
<td>Morbidly obese</td>
<td>&gt; 40</td>
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</table>

1998-2010 n=14,084 (83% men)

• Median BMI at ART initiation rose from 23.8 to 24.8
• The percentage of HIV group with obesity rose from 9 to 18%

Temporal trends in obesity in treated HIV

Three years after starting ART

• 22% of those with normal BMI at baseline were overweight
• 18% of those overweight at baseline were obese
Contemporary ART is associated with fat gain  
Mean (97.5% CI) percent change in VAT (ITT): ACTG 5260s

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<tr>
<th>VAT Change</th>
<th>ACTG 5260s</th>
<th>ATV/r 31%</th>
<th>RAL 33%</th>
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Change in Waist Circumference on ART at 96 Weeks  
ACTG 5257 (n= 1,814)

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<td>Week 96</td>
<td>97</td>
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Interventions to Reduce Non-AIDS Events in HIV

• Lifestyle interventions
  • Smoking cessation
    • Smoking may synergize with HIV to increase mortality
  • Screen and treat for hypertension, diabetes
  • Diet and Exercise (1-3)
  • Earlier ART


HIV+ Individuals in Care No Longer Have Elevated MI Risk compared to controls(2010-2011), Kaiser Cohort

- Cohort to evaluate MI risk from 1996 to 2011 by HIV status
- Adjusted MI rate ratio for HIV status declined over time, reaching 1.0 (95% confidence interval, 0.7-1.4) in 2010-2011 (most recent period)

<table>
<thead>
<tr>
<th>Calendar Year</th>
<th>HIV-positive</th>
<th>HIV-negative</th>
<th>Rate Ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>1996-1999</td>
<td>276</td>
<td>136</td>
<td>1.8 (1.2-2.6)</td>
</tr>
<tr>
<td>2000-2003</td>
<td>324</td>
<td>162</td>
<td>1.7 (1.2-2.3)</td>
</tr>
<tr>
<td>2004-2007</td>
<td>270</td>
<td>178</td>
<td>1.3 (1.0-1.6)</td>
</tr>
<tr>
<td>2008-2009</td>
<td>245</td>
<td>167</td>
<td>1.3 (1.0-1.7)</td>
</tr>
<tr>
<td>2010-2011</td>
<td>195</td>
<td>165</td>
<td>1.0 (0.7-1.4)</td>
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HIV-1 Interventions
- Anti-fibrotics? IL-7?
- HIV-1 Infection Immunodeficiency
- Microbial Translocation
- Viral Reactivation (eg, CMV)
- Innate Immune Activation (MØ/DC)
- T Cell Turnover, Activation, Lymphoid Fibrosis
- Functional T Cell Defects / CD4+ Lymphopenia
- Infections, Malignancy
- Inflammatory Cytokine Secretion (eg, IL-6, TNF-α)
- Cardiovascular, Renal, and Liver Disease, Osteoporosis, Frailty, Cognitive Dysfunction
- TLR 7,8 Activation?
- Tissue Factor, Clotting Thrombosis, CAD/Stroke?
- IDO-1 induced Tryptophan Catabolism
- T Cell Proliferative Defects
- Th17 depletion
- Rifaximin (A5286)
- Sevelamer (A5296)
- Chloroquine (A5258)
- Novel CMV Drugs?
- Other TLR Inhibitors?
- LD-Methotrexate (A5314)
- IDO-1 Inhibitors?
- Probiotics (A5350)
- Prebiotics?
- IL-1 inhibitors: Canakinumab
- TNF-α inhibitors
- IFN-α Inhibitors
- Ruxolitinib (A5336)
- STATINS (A5332)

Progress in Developing Interventions to Target Novel Pathways "Probe" Studies

Slide credit: Peter Hunt
IL-1β inhibition in HIV

- Canakinumab is a monoclonal antibody directed against IL-1 β, approved for use in inflammatory diseases including JRA, FMF
- Currently being studied in a trial of 17,200 HIV negative adults with CVD to test whether reducing inflammation decreases future CVD events (CANTOS)
- HIV Pilot study led by Priscilla Hsue
  - NHId funded: Hsue, Deeks, Ridker, Tawakol
  - N=100 individuals randomized 2:1 treated with 150mg canakinumab at baseline and at 12 weeks, followed for 36 weeks, measuring arterial inflammation with FDG-PET

Ruxolitinib

- Ruxolitinib is an FDA approved Jak2 inhibitor that disrupts the Jak-STAT pathway.
- This pathway is thought to be upregulated in HIV infection and may contribute to the production of pro-inflammatory cytokines, notably IL-6 and TNF-alpha
- This is a proof of concept study with only 5 weeks of drug exposure
- Participants must have CD4 > 350, be suppressed with good renal function and not on boosted PI
Statin use in HIV: Which statement best reflects your current view

1. I follow current AHA/ACC guidance for use of statins without modification for patients with HIV
2. I prescribe statins to patients with HIV without regard to current guidelines
3. I don’t know what we should be doing about the use of statins in patients with HIV

THE REPRIEVE TRIAL TESTS A STRATEGY TO PREVENT HEART DISEASE IN HIV

“RANDOMIZED TRIAL TO PREVENT VASCULAR EVENTS IN HIV”

REPRIEVE is the first large-scale randomized clinical trial to test a strategy for preventing heart-related disease among people living with HIV.

Statin clinical endpoint trial in HIV
- Statins reduce inflammation
- Pitavastatin has no interactions with ART
- Patients with treated HIV who do not meet criteria for statins will be randomized to pitavastatin or placebo

- 6500 patients
- 108 sites globally
- Mechanistic Substudy to examine CT Angio outcomes
- Substudies on sex differences, renal outcomes and muscle function

Funded by NHLBI and NIAID. Supported by KOWA Pharmaceuticals.
Summary

• Non-AIDs events are a growing cause of morbidity and mortality in treated HIV in all settings
  • Inflammation and the innate immune activation appear to be contributors; biomarkers may have utility in predicting risk and informing interventions
  • Traditional risk factors remain important
  • Fat gain on ART may represent a "return to health" but obesity is a growing concern
• New interventions to reduce inflammation for patients on ART under evaluation
• Impact of newer ART agents warrants investigation

Thank-you!

• UCLA CARE Center Team
  • Jordan Lake (now at UT Houston)
  • Peter Hunt
  • Priscilla Hsue
  • Peter Reiss