## CV complications of HIV Infection? Lessons learned from other inflammatory conditions *in children and adolescents*



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# **Questions:**

- •Why should we worry about CVD?
- •How do CV risk factors influence development of CVD across the lifespan?
- •What conditions are associated with chronic inflammation in youth?
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#### Why? Should Non-Cardiologists Care About Atherosclerotic CV Disease?

#### Health Care Costs (in billions of dollars)



- •CVD accounts for 1/3 all cause mortality worldwide
- •Costs billions of dollars
- •Only 1% CVD due to Congenital Heart Disease

WHO World Health Statistics 2013; Rosamond Circ 2007; figure = Mozaffarian 2016 Hospital Medica

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#### Time Course for Development of Atherosclerosis: *Aging Begins at Conception*



• Atherosclerosis is a slow process that begins early in life and is accelerated by adverse levels of CV risk factors such as obesity, HTN, dyslipidemia and insulin resistance Cincinnation

#### **But Does Actual** Atherosclerosis Develop in Youth?



•Thicker renal arteries



\*P<0.01 for trend, N = 204, 2-39 years; Berenson, NEJM 1998.

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## Measurement of CVRFs Should Start in Youth



• Elevated CVRFs exist in Youth: Levels differ from adults, change with rapid growth, but CVRFs 'TRACK' so are helpful to predict adult levels & CVD.



#### **Childhood BMI Predicts Metabolic Syndrome as Adult**



• Ability to predict diagnosis of Metabolic Syndrome as Adult increases with increasing Childhood BMI & insulin level.



Mean f/u 11.6 yrs; Srinivasan Diabetes 2002; N = 745, 8-17 yrs @baseline.



•Meta-analysis of 4,633 subjects found correlation between BMI & CRP was 0.36 in adults & 0.37 in children.

Choi 2013 Obes Rev



#### Leukocytes Link Inflammation to Ischemic CV Disease



•New research uncovered unsuspected inflammatory signaling networks that link the brain, ANS, bone marrow, & spleen to atherosclerotic plaque & infarcting myocardium

#### Inflammation is Associated With Hard CV Events



•>20 prospective studies have shown CRP independently predicts CVD and 6 cohort studies have confirmed CRP adds incremental value beyond traditional CVRFs.

Ridker 2004 Circ



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**Conditions Associated with Chronic Inflammation** *In* **YOUTH** 

- •OBESITY (especially with related IR)
- •Infections: HIV, peridontitis
- •Rheumatologic conditions: arthritis, SLE
- •GI: IBD, Crohn's
- •Pulmonary: Asthma
- •Vasculitis: Kawasaki, transplant rejection
- •Diabetes Types 1 and 2
- •Renal Disease



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#### What Should We Measure To Evaluate CV Risk Related to Inflammation?

**Inflammatory Markers** 

Test	<b>Relation to CV TOD</b>
WBC	No Data
ESR	FMD (JIA), cIMT (Fam Med Fever , normals)
CRP	PWV (smoke, IR), IMT (O, T1DM, BP) NEGATIVE: FMD, IMT (FH)
IL-6	<b>PWV (APSGN)</b> NEGATIVE: RHI
TNF-α	No Data
SAA	cIMT (Fam Med Fever, normals) NEGATIVE: cIMT

#### What Inflammatory Markers Should be Measured? Markers Related to Inflammation

Test	<b>Relation to CV TOD</b>
<b>Myeloperoxidase</b> (leukocyte activation)	NEGATIVE: RHI
Adiponectin (adipocytokine)	cIMT (O, normal)
Fibrinogen (clotting)	cIMT (FMF, normals)
sICAM-1 (leukocyte adhesion molecule)	cIMT, FMD NEGATIVE: cStiff (O, BP)
sVCAM-1 (leukocyte adhesion molecule)	<b>Correlates with BP</b> NEGATIVE: no correlation with BP
<b>P-selectin</b> (leukocyte adhesion molecule)	cIMT (FH)
<b>E-selectin</b> (leukocyte adhesion molecule)	cIMT (O, BP) NEGATIVE: FMD

Hospital Medical Cente

#### **Non-Invasive Methods** *to Assess Atherosclerosis TOD*



- Carotid US (IMT)
- Arterial stiffness (PWV)
- Endothelial function (FMD)

All predict future CVD







Stein JASE 2005 & Gepner JASE 2006; Bots Stroke 2003



- Higher PWV (stiff) associated with 48% increase in CVD risk above & beyond traditional CVRFs
- Higher cIMT predicts Stroke & MI
- Low FMD associated with greater CV Events in Met S patients over 6.75 yr f/u.

N=2232, 63 years, 58% women; Mitchell 2010 Circulation; O'leary NEJM 1999; Suzuki 2008 Am Hart Medical Cer

#### Intima-Media Thickness with Arterial Ultrasonography



- •Can Image Common, Bulb, Internal Carotid or Femoral
- •Use 'Meyer's Arc' for Longitudinal Studies



Stein JASE 2005 & Gepner JASE 2006; Bots Stroke 2003



- •cIMT measured in young adults.
- Those with thicker carotid arteries (solid line) were significantly more obese as children even after adjustment for Chol & BP.
- Differences in BMI demonstrated starting around age 10

Freedman & Urbina, Int J Obese 2003, N=513, P<0.05.



- Subjects from BHS, Muscatine, Young Finns, Muscatine & Childhood Determinants of Adult Health (Australia) combined.
- Childhood lipids classified as normal, borderline or high based on both NCEP and NHANES cutpoints
- Regardless of definition used, high childhood LDL & low HDL predicted thicker cIMT as adult (age 29-39 years).

Magnussen JACC 09



## Multiple CVRFs in Youth Affect the Adult cIMT Young Finns Study



Number child CVRFs was associated with 6-year change in adult cIMT even after adjusted for adult CVRF and genotype.
Infrequent fruit and low physical activity were the most powerful in predicting accelerated progression.
CRP & SAA not independent contributors.

N=1809; age 3-18, followed 27 years; Juonala 2010 Eur Hrt J; Juonola 2006 ATVB; Hylahava 2008 JintMed



#### Abnormalities in Carotid Structure & Function *in Kawasaki Disease*



•Significantly thicker and stiffer carotid in Kawasaki Disease patients despite being matched for BMI, BP, & lipids suggesting a role for inflammation-induced vasculitis.

> Cincinnati Children's Hospital Medical Center

\*P<0.05, N=20 KD, 20 Control, age 16.6 years, Noto Pediatrics 2001

#### Higher Carotid Intima-Media Thickness in Youth with JRA



•Subjects with newly diagnosed JRA had higher cIMT than controls associated with higher myeloperoxidase (MPO) levels.

N=39 JRA, 27 control, mean 13 yers; l Ilisson 2015 Arthitis Res Ther





•Progressive increase in carotid IMT from normal to obese to obese youth with metabolic syndrome.



P<0.01 vs control; Akyol 2013 J Clin Res Ped Endo

#### Weak Relationship Between CRP & Carotid IMT in Youth



Non significant trend for increased Carotid & Femoral IMT across hsCRP tertiles.
hsCRP correlated to IMT but only in sedentary group.

N= 120, mean 11.7 years, Cayres 2015 J Peds



# Relationship Between CRP &IMT Overshadowed by CVRFs in Youth



- •Subjects with CRP >95<sup>th</sup>%, had higher CVRFs (BMI, BP, LDL, glucose, insulin, HbA1c) & thicker cIMT.
- •CRP only remained an independent determinant of carotid bulb after adjustment for BMI & fasting glucose, but lost significance after adjustment for other CVRFs.

N=670; mean age 18 years;  $p \leq 0.04$ ; Urbina unpublished data



#### **Effect of Inflammation on cIMT Increases With Follow-up into Young Adulthood** 0.8 <sup>=</sup>ollow-up Bulb (mm) 07 0.6 0.5 0.4 0.3 .2 $\mathbf{0}$ -15 5 -10 -5 10 0 15 Change in CRP (mg/dl)

Study Group — Lean — Obese — T2DM

- •After 4 yrs follow-up, increase in CVRFs (BMI, BP, lipids, insulin, CRP) & cIMT.
- •CRP change <u>did remain</u> independent determinant of followup bulb after CVRF adjustment. Effect strongest in O & T2DM. Maybe due to longer duration of exposure.

#### **Does Inflammation Effect IMT**

**Directly** In Adolescents?



- •Structure Equation Modeling explains more of the variance in IMT (25-50%), but also demonstrates that obesity & inflammation only have indirect effects through increases in other CVRFs.
- •Largest direct effect were age , BP, Glucose, non-HDL.

Gao, Urbina Atherosclerosis 2016; N 784, age 10-24 years, 1/3 L, 1/3 O, 1/3 T2DM

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#### **Increased cIMT** *With Oxidation of LDL*



- May need combination of inflammation & other CVRFs.
- Inflammation induces oxidation of LDL increasing atherogenesis. DCCT/EDIC subjects with obesity & longer duration of T2DM had higher levels of oxLDL
- 6x greater Odds for being in highest quartile of cIMT at f/u with elevated oxLDL even after adjustment for CVRFs.
- oxLDL better predictor than LDL-C.

Diabetes Control & Complications /Epid of Diab Intervent Complicat) N=494; Lopes-Virella 20 Ichildren's Diabetes

#### **Reduced Carotid Distensibility** *With Increased Inflammation Score*



•Composite inflammatory score (CRP, SAA, IL6, IL8, TNF α, sICAM1) was related to higher carotid stiffness even after adjustment for CVRFs in elderly.

\*All P < 0.001; Van Bussel 2012 J Hypertens



#### **Pulse Wave Velocity** *Higher PWV = Stiffer Vessel*







Carotid

- Carotid-Femoral distance measured with caliper
- Pressure waves recorded at the carotid & femoral arteries with tonometry, photoplethysmography.
- Time measured from R on ECG to foot of pressure wave

Λt

• Calculate **PWV** = <u>distance</u>



T<u>ime</u> 1

#### **Increased PWV**

With Acute Post-Strep Glomerulonephritis



•16 children with APSGN were found to have higher baPWV as compared to controls.

•Recovery led to normalization of BP and arterial stiffness.



Yu Pediatr Nephrol 2011

#### **Stiffer Aorta (Higher PWV)** In Children with Inflammatory Connective Tissue Disorders



• Children with Inflammatory Connective Tissue disorders such as Lupus were also found to have stiffer thoracic aorta despite concurrent treatment with Aspirin

\*P<0.02 Marfan & CT > Control; Sander JASH 2003



## **Higher PWV**



In Youth with Obesity & Metabolic Dysfunction



- •Higher PWV in Obese youth with further increase in Obese Insulin-Resistant, Severe Obesity and subjects with T2DM.
- •CRP not independent determinant in any of the studies. Urbina Diabetologia 2011; Urbina J HTN 2010; Shah & Urbina JCEM 2015; All differ from L. Childre



Baseline Follow-up

- Over 5 years of follow-up, PWV increased only in O & T2DM subjects.
- Independent determinants of change in PWV included measures of adiposity, BP, LDL and glycemic control. CRP did not enter the model.

\*P for difference among groups in change over 5 years  $\leq 0.05$ ; unpublished data Urbina 2016.
#### **Higher PWV** in Youth with T2DM Related to Inflammation



Chinese youth with newly diagnosed T2DM who had low grade inflammation (higher CRP) had higher IMT.
hsCRP remained independent determinant after adjusting for CVRFs.

N=98, age 10 to 24 years, Li 2015 JClinResPedEndo





- No association was found between inflammatory markers and progression of PWV in the arm or leg.
- •Fibrinogen & inflammation composite score were weakly associated with progression of carotid-femoral PWV (trunk), but associations were attenuated after adjustment for other **CVRFs**

Alman, unpublished data 2014; p for increase 0.0001



### **Brachial Flow Mediated Dilation** *For Evaluating Endothelial Function*



Image Brachial Artery
Inflate cuff to 50 mmHg > SBP for 5 min, then deflate rapidly
Record post-deflation images immediately & at 60, 90 & 120 seconds.

•Calculate *FMD* = %change in diameter



Non-US methods also developed (RHI-PAT, LFD)



### **Peripheral Arterial Tonometry**

Non-Ultrasound Assessment of Endothelial Function







#### **RHI** = **PAT** post occlusion / **PAT** baseline (normalized to control hand)

- Finger cuff placed on index finger of each hand, connected with tubes to device which is interfaced to PC.
- •Balloon in cuff inflates to sense changes in blood volume at baseline & after ischemia (cuff inflated 5 minutes like with FMI

Itamar, Inc., Caesarea, Israel

#### **Reduced Endothelial Function** *After Kawasaki Disease*



•Endothelial function measured by Peripheral Artery Tonometry Reactive Hyperemic Index was lower in young adults who suffered Kawasaki disease as a child.

N=16 cases, 19 controls; Pinto 2013 Carioil Young



### **No Difference in Endothelial Function** *In Adults with Lupus*



• No differences in FMD or RHI between SLE and control even in severe SLE with Reynaud's.



N = 58, Aizer 2009 Lupus

#### Impaired FMD in Obese Children Related to Inflammation



- •FMD lower in obese youth
- •FMD correlated with higher CRP level in univariate analyses. Did not repeat adjusted for other CVRFs.

N=77 Obese, 15 lean; Kapiotis 2006 ATVB



#### Impaired FMD in Healthy Children Related to Inflammation



- •FMD declined with increasing CRP level even in healthy youth.
- •SD of FMD ranged from 2.6 to 4.4 so much overlap & did not adjust for other CVRFs.

Jarvisalo Art Thromb Vasc Biol 2002, N=79, Age 9-12 years, \*P<0.05 between CRP groups.



### **No Relation of FMD to Inflammation** *In Healthy Adolescents*



•No relation between CRP & FMD in healthy youth.

N=55, Urbina unpublished data 2017



### Why Does Vascular Dysfunction Matter? Because it Hurts the Heart

Artery



Normal Artery



Cincinnati

#### **Stiffer Vessels Cause Thicker Heart** 60 50 **VMI** (g/m<sup>2.7</sup>) **40** $R^2 = 0.52, p \le 0.0001.$ 30 20

10 1 2 3 4 5 6 7 Global Arterial Stiffness Index Score

•Measures of central & peripheral arterial stiffness combined.

- •Global Stiffness Index independently related to LVM Index even after adjusting for CV risk factors.
- •Subjects with stiff vessels had higher CRP, however CRP not independent determinant of LVM.

\* $P \leq 0.0001$  slope differs from 0; Urbina J Peds 2011



### **Decreased Diastolic Function** *with Increased Arterial Stiffness*



- •Linear decline in Diastolic Function (lower e'/a') with stiffer arteries even after adjustment for other CV risk factors.
- •Diastolic function may be a precursor to CHF in adults.
- •CRP was not an independent determinant.

Madsen, Urbina, unpublished data 2017, \*P<0.01



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#### **Carotid IMT** *Predicts Mortality in Adults with HIV*



- Higher IMT (& CRP) predicted reduced survival after only 3 years of follow-up in adults with HIV.
- Death associated with lower CD4 count, higher viral load, & CRP, but not antiretroviral regimen.



N=327, Mangili 2011 Atherosclerosis

## Factors Influencing CVD In HIV



- Direct: infection or activation of endothelial cells by HIV
  Indirect: vascular injury due to inflammation & immune activation, dysregulation of NO.
- •Rx: HAART alters lipid, glucose, and fat metabolism *Mondy 2008 J Cardiometab Syndr*



### **Decreased Distensibility** In Adults with HIV related to T-cell Activation



- CD4+CD38+HLA-DR+ T cells, %
- Higher T cell activation was associated with lower carotid distensibility even after adjustment for age, medications, CVRFs, CD4 count & viral load.
   Confirmed in later study

N=114 cases, 43 controls; Kaplan 2011 Atherosclerosis; Karim 2014 JAIDS



### Increased IMT & Inflammation In Adults with HIV



Subjects with HIV had higher levels of inflammatory biomarkers (CRP, TNF alpha, IL-6, MPO, sICAM).
Also had higher IMT which correlated with hsCRP.
But in multivariable models, only TNFa, MPO & sVCAM were independent determinants of IMT, not CRP

N= 73 cases, 21 controls; Ross 2009 Clinical Infectious Diseases



### **Decreased Distensibility** *In Adults Related to HIV Rx*



- •Lower Aortic Distensibility in HIV+ infected patients vs controls (worse if >=40 years) but no difference in c-IMT.
- Multivariable analyses: HIV infection independently associated with decreased distensibility & among HIV-infected patients distensibility declined with increasing duration to HAART exposure. N=155 cases, 124 control; Zomplala 2012 BMC Infect Dis

### **Increased IMT Associated with CD4 Nadir** *In Children with HIV*



•IMT thicker in youth with HIV even when included subjects who are virally suppressed.
•Patients with lower CD4 nadir had higher IMT which remained significant determinant of IMT after adjustment.
•No relation b/t IMT & inflammation or immune activation is Sainz 2014 J Acquir Immune Defic Syndr



Higher IMT in children with HIV.
Independent determinants were ART, Adiposity, & CD4 count.

N=83 cases & 83 controls; Giuliano Coronary Art Dis 2008; \*P<0.001.



### **Higher IMT**

In Children with HIV related to ART Rx



- •IMT higher in HIV+ vs controls regardless of measurement site.
- •Predictors: BMI, homocysteine & ART Rx.

N=31 cases, 31 controls; McComsey AIDS 2007; \*All P<0.02.



### **Type & Duration of ART Influences IMT** *In Children with HIV*



•Higher IMT seen in subjects with HIV associated with male sex & duration ART Rx but only significant for Non Nucleoside RTI &/or PI + single/double NRTI

N=23 cases 19 controls age 17-23 years; Vigano Current HIV Res 2010



### Not All Studies Show IMT Related to HIV Rx



- •Although cIMT higher in HIV vs controls, strongest influence was age.
- •No independent association b/t IMT & any specific antiretroviral, viral load, CD4 count or CRP.
- •Considerations: small N, only common carotid

N=40 cases, 27 controls; Di Biaggio J Ultrasound Med 2013



### Not All Studies Show Higher IMT In Children with HIV

Parameter	Common	Internal
	ß Estimate	ß Estimate
Age	0.01	
Sex		-0.63
CRP	< 0.01	< 0.01
<b>R</b> <sup>2</sup>	0.41	0.35

- Though hsCRP was higher in subjects with HIV, no difference in IMT between groups
- Predictors of IMT were age, female, hsCRP.
- Issues: small N, younger age



N=27 cases, 30 controls mean 11 years; Ross McComsey Atherosclerosis 2010

## **No Difference in Rate of Change in cIMT** *In Children with HIV*



Same group increased N & saw HIV+ had higher baseline IMT (common & ICA). IMT △ over 48 wks was not significantly different between groups but most virally suppressed. Determinants CRP, ART, CD4
Further f/u to 144 wks also saw no difference in IMT △ cincinati N=35 cases, 37 controls, median 10 years; f/u 44 wks Ross Ped Infect Dis J 2010; Ross Antivir Ther 2005 Performed

### Increased Arterial Stiffness In Children with HIV



- •No difference in IMT but carotid stiffness was greater & FMD lower in HIV.
- •No difference by ART Rx or presence of dyslipidemia.
- •Considerations: small N, only common IMT



*N=49 cases, 24 controls; Bonnet AIDS 2004; \*P*<u><0.0001</u>.



- •PWV higher in HIV +.
- •Associated with ART, SBP, disease severity, Tchol.
- •Considerations: carotid-radial PWV, large SD of measurement.

N=83 cases, 59 controls; Charikida Antiviral Therapy 2009; \* P<0.04 vs control, Children's

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### **Lower Brachial FMD** In Adults with Higher Viral Load or Inflammation



Matched by CVRFs, subjects with HIV had lower FMD related to viral load & TNF alpha.
Other study found lower FMD with lower nadir CD4 count

N=38 cases, 41 control; Oliviero 2009 Atherosclerosis; Ho 2012 AIDS

### **Reduced Endothelial Function** *In Children with HIV*



FMD lower by 1.8% for non-Rx and 3.6% for PI.
FMD related to CRP & ART exposure, not lipids despite higher lipid levels in cases.

N=83 cases, 59 controls; Charakida Circ 2005; \* and \*\*  $P \leq 0.006$ .



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- •Youth with low levels of CV risk factors in childhood had *lower carotid IMT* as an adult.
- •Similar results found in CV Risk in Young Finns
- Neither had measure of inflammation

\*P< 0.01, N=1474, 4-17 years at baseline, 19-41 years at follow-up; Chen Diabetes Care 2005; Cincinnati Laitinen Circulation 2012; Magnussen JACC 2012.

## Lifetime Fruit & Veg Consumption And PWV as Adult



- CV Risk in Young Finns Study followed for 27 yrs.
- Persistently high consumption of fruits or vegetables associated with lower PWV vs persistently low.
- No measure of Inflammation.

N=1622, age 3-18 years at baseline; Aatola 2010 Circulation



## **Improvement in FMD** with Recovery from Metabolic Syndrome



- FMD measured in 1673 subjects in the CV Risk in Young Finns Study
- After 6 years, recovery group had higher FMD compared with the control group and better CRP.



\*P<0.03; N=1673 31.5 years at baseline, Koskinen 2010 Circulation

### "Primary Prevention" Weight Loss Improves Inflammation in Obese Youth



- 2 week in-pt low calorie diet, & supervised daily physical activity dropped BMI, BP, TG & CRP.
- 3 mo out-pt intensive lifestyle had little drop in BMI but significant decrease in CRP & IL-6

N=18, mean 13 years; Roberts 2007 Atherosclerosis, N=15, mean 16 yrs Balagopol 2005 JPeds Children Herosclerosis, N=15, mean 16 yrs Balagopol 2005 JPeds

#### **Change in Inflammation** *Lifestyle & Supplements*

Test	$\Delta$ w/ Intervention	No Change
WBC		↑post exercise, No ∆Omega3
CRP	↓ Wt loss	No ∆Omega3; No ∆exercise but ↑FMD; giving DHA or Vit E & C no effect on CRP but ↑FMD
IL-6		<b>↑post exercise, No</b> ∆exercise
TNF-α	↓∆Omega3	↑post exercise; No ∆exercise
SAA		No ∆Omega3
sICAM		No ∆Omega3; No ∆exercise
sVCAM	↓ ∆Omega3	No ∆exercise
APN	<b>↑Wt loss</b>	No ∆exercise



#### **Improvement in HOMA-IR** Leads to Regression of IMT in Obese Adolescents



- •One-year weight loss resulted in improvement in CVRFs & regression of IMT.
- Change in HOMA-IR was negatively correlated with change in cIMT independent of other CVRFs.

N=29, r=0.41, P=0.03; de Lima Sanches Hypertens Res 2011;34:232-8.


#### IR Impairs Ability to Regress IMT With Weight Loss



#### Improved IR IR persisted •After 1 year Wt loss program, subjects with IR had less regression of cIMT than insulin sensitive group despite larger drop in BMI in IR group.

 $N=66; P \le 0.05$  \*difference from baseline, †Difference by IR status; Sanches Arq Bras Cardiol. 2012;99:892-8.



#### **Improved Brachial FMD** With Exercise in Youth with Metabolic Syndrome



- •Obese children randomized to 8 weeks of exercise or control group.
- •Post intervention there was significant improvement in FMD despite no change in CRP.



N = 25, 10-11 years, Kelly J Pediatr 2004

## **Greater Improvement in Vascular Function** *With Both Diet & Exercise*



- •Obese youth randomized to Diet or Diet & Exercise for 1 year.
- •Both groups had significant improvement in WHR, Tchol & FMD.
- Diet & Exercise saw greater increase in FMD that returned towards baseline at 1 year if exercise discontinued.

\*p < 0.002 vs baseline, †p < 0.01 vs diet alone,  $\ddagger p < 0.04$  greater than 6 mo, N = 82, age 9-11 years; Woo Circ 2004 Hospital Medical Control of the second secon

## Relation Between Exercise Inflammation & Art Stiffness in Adults with T2DM



•Adults with T2DM with greater physical activity (pedometer) had lower BMI, CRP, IL6 & PWV.



\*P < 0.007 for trend, N=327; Jennersjo 2012 Diabet Med

## Improvement in PWV with Statins in Inflammatory Joint Disease



- Adults with Inflammatory Joint Disease (CRP 2 mg/l) Rx with Rosuvastatin for 18 months.
- Improved PWV
- Did not measure inflammation. N=89. Ikdahl 2016 PLoS ONE





• Treatment of youth with FH with Simvistatin led to normalization of FMD after 28 weeks.

De Jongh, JACC 2002, N=69, age 9-18 years, \*p<0.05 baseline vs follow-up.



## **Improvement in Endothelial Function with Vit C** *After Kawasaki's*



- •FMD in Kawasaki disease patients was significantly lower than controls.
- •IV Vitamin C significantly increased FMD in KD patients vs placebo.
- •Other studies found no difference in FMD (Silva J Peds 2001)

N= 39, P<0.0001 \*difference from control, †difference from placebo ; Deng 2003 Ped Inf Dis

## **Association of Vitamin D** *with Vascular Function*



- Low Vit D associated with lower FMD & RHI even after adjustment for CVRFs including CRP.
- No interventional studies have proven Vit D supplementation will improve endothelial function.



N=554 Al Mheid 2011 JACC

## **Less IMT Progression** In Virally Suppressed Adults with HIV



- •Lower progression with viral suppression.
- Lower progression with nonnucleoside reverse transcriptase inhibitor versus protease inhibitor exposure was associated with lesser CIMT. Cincinnati

N=389, mean 42 years; Baker 2011 Clin Infect Dis



## **Normal PWV** *In Virally-Suppressed Adults with HIV*



•Virally suppressed HIV-infected patients showed similar arterial stiffness to non-HIV-infected patients
•No HIV + group without viral suppression.

N= 81 control, 174 cases; Eschieverria 2014 J AcqImmDefS





- •No difference in rate of change in IMT over 2.8 years among Controls, subjects with HIV on a PI or those not on a PI
- Predictors of progression were nadir CD4 count & use of ritonavir

Cincinnati Children's Hospital Medical Center

N=134 total, Currier 2007 AIDS

# Diet May Affect Carotid Atherosclerosis *in Adults with HIV*



Subjects with HIV but without atherosclerosis (IMT <0.09) had higher Med Diet Score. Only trend for Controls.
No Rx trials proving lack of progression with healthy diet.

\* p= 0.04, N= 73 cases, 21 controls; Ross 2009 Clinical Infectious Diseases

#### Lower Carotid IMT With Higher Vitamin D in Adults with HIV



•52% of these adults with HIV had Vitamin D deficiency.
•Graded increase in cIMT seen across Vit D level even after adjustment for CVRFs & HIV related factors.
•No Rx studies to prove supplementation will improve IMT. N=139, mean 45 years; Choi 2011 Clin Infect Dis

## **No Significant Increase in FMD** *With Rx with Omega-3 FA in Men with HIV*



- •Subjects with HIV Rx with Omega 3 FA 2000 g/day had no increase in FMD after 24 weeks.
- •Issues: very small N, sub-therapeutic dose of Omega 3

N=17 placebo, 14 Omega 3; Hilerman 2012 AIDS Res Human Retro



## **Improved Arterial Cp & HRV** *With Exercise in Adults with HIV*



•Subjects with HIV who were fit had greater Arterial Compliance (lower arterial stiffness) than either subjects with HIV who were unfit or Healthy subjects who were unfit.

Spierer Clin Auton Res 2007; all \*P<0.05.



# Summary

#### • Which inflammatory biomarker to measure

• Most data available relating CRP to TOD but results not consistent.

#### • Target Organ Damage:

- CRP has most studies
- Stronger relation to cIMT & Arterial Stiffness than FMD
- Few studies show effect independent of other CVRFs

#### •Interventions:

- Exercise, wt loss, diet may help but results inconsistent
- Supplements not clearly helpful
- Statins may help
- Lack of 'normals' for intermediate vascular outcomes = hard to know when to intervene



## Limitations

- Innate biologic variability in methods (FMD) may contribute to lack of correlation of inflammation & TOD
- •Longer duration/degree of inflammation may be needed to see effect.
- •May need more advanced statistical techniques (structure equation modeling) to tease out the independent effects of inflammation (BMI dominates models).



## **CAD Risk Classification**

#### **Minimal Risk**

No identifiable risk factors

## **Very Slight Risk**

One risk factor of moderate degree Several risk factors of only mild degr

#### **Slight Risk**

One risk factor of advanced degree Several risk factors of moderate degree

#### **Moderate Risk**

Two risk factors of advanced degree

#### **Serious Risk**

Three or more risk factors of advanced degree

CV disease & Chest Pain, 1993





# **Consider Non-Invasive Imaging** *For Risk Stratification*



#### **Carotid Plaque**



## Consequences of Ignoring the Problem





#### Left Ventricular Hypertrophy

**Myocardial Scar** 

Cincinna

http://upload.wikimedia.org/wikipedia/commons/b/ba/Heart\_left\_ventricular\_hypertrophy\_sa.jpg

Questions?