

Nutritional, Metabolic, and Gastrointestinal Complications in Pediatric HIV Infection

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I have no financial relationships with any
commercial entity to disclose

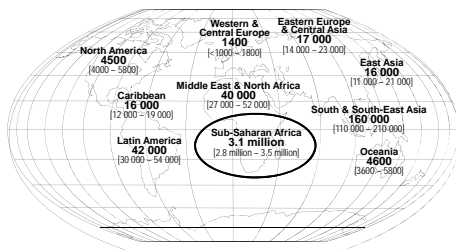


Outline

- Epidemiology of Pediatric HIV: developed and developing nations
- HIV and the GI tract: Pre-HAART era
- HIV and the GI tract: HAART era
- Clinical consequences associated with GI tract-associated immune activation
- Future therapeutic considerations

Epidemiology of Pediatric HIV A Global Problem

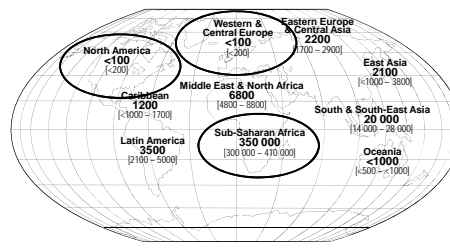
Children (<15 years) estimated to be living with HIV | 2010



Total: 3.4 million [3.0 million – 3.8 million]

WHO/UNAIDS 2010 (most recent data)

Children (<15 years) newly infected with HIV | 2010

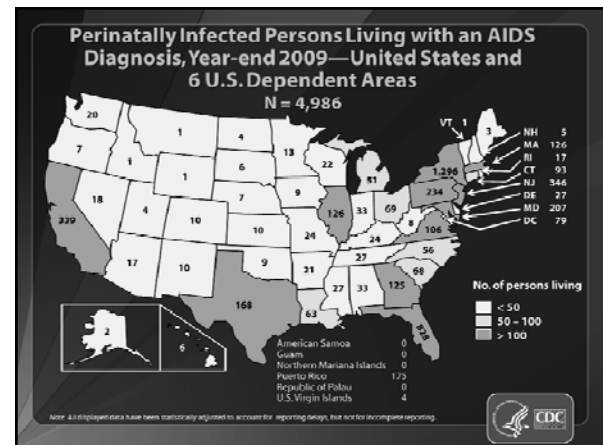
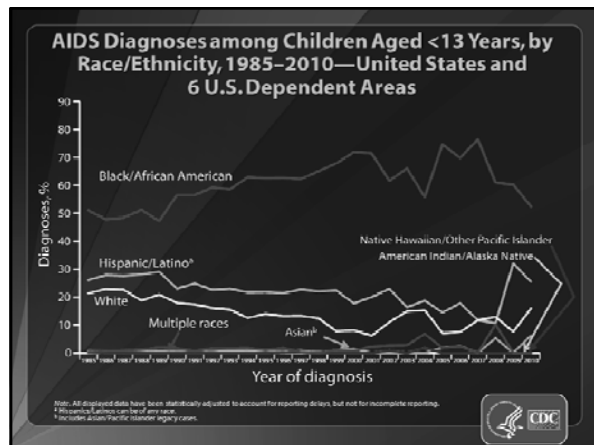
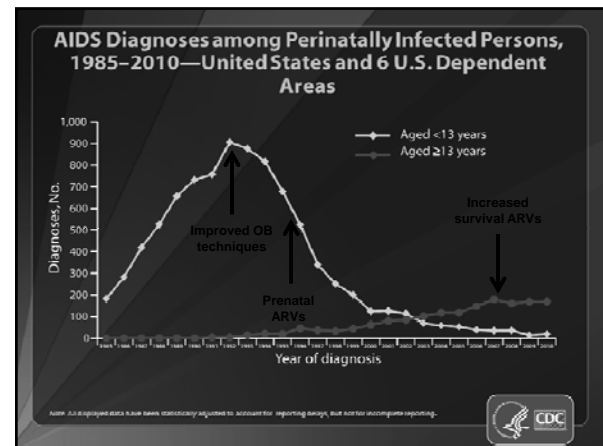


Total: 390 000 [340 000 – 450 000]

WHO/UNAIDS 2010 (most recent data)

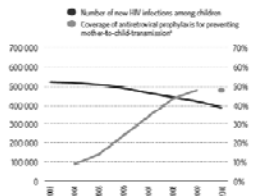
Epidemiology of Pediatric HIV

Developed Nations:
Effects of ARVs



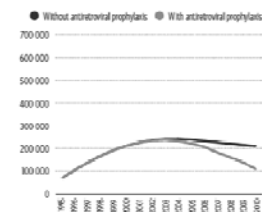
Perinatal Transmission of HIV is Decreasing with Greater Availability of ARVs

Fig. 1.2 Coverage of antiretroviral prophylaxis for preventing the mother-to-child transmission of HIV and the number of new HIV infections among children, low- and middle-income countries, 2003-2010



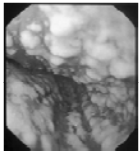
WHO Progress Report, 2011

Fig. 2.11 Number of new HIV infections among children in low- and middle-income countries 1995-2010

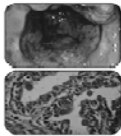


HIV and the GI Tract: Pre-HAART Era

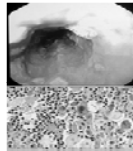
Emergence of Lesions in the GI Tract: CD4 Counts <200 Confer Greatest Risk



Candida esophagitis



CMV Colitis



Herpetic ulcer

Other infectious agents:

Cryptosporidium
Toxoplasmosis
Idiopathic ulcers
To name a few...

Cello: Medscape Education
and Healio.com

HIV and the GI Tract: Pre-HAART

- **Portal of Entry:** The GI tract initially gained attention as the primary portal for entry/infection in humans
- **Clinical Disease:** Kotler et al (1984) was one of the first to describe an "HIV enteropathy" in 12 adults
 - Villous atrophy/blunting
 - Crypt hyperplasia
 - Inflammatory infiltrates in lamina propria
 - Absence of infectious agent
- Further studies: Impaired absorption and regeneration, increased mucosal permeability

Normal vs HIV Gut

Normal

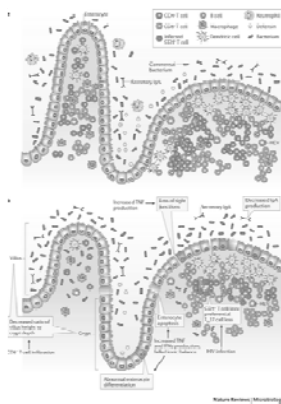
Tight junctions - intact

slgA
TH17
Defensins

Prevent
Bacterial
overgrowth

HIV+

Depletion of CD4 (90% depleted in 2 wks)
Increased CD8; Decreased TH17
Increased IFN, TNF – destruction
of tight junctions
Decreased villous height
Increased apoptosis
B cell dysfunction – low slgA
Bacterial overgrowth

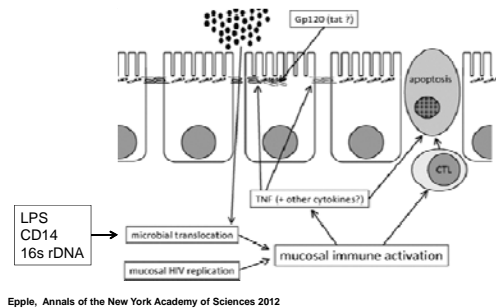


Sandler, Nature Reviews, 2012

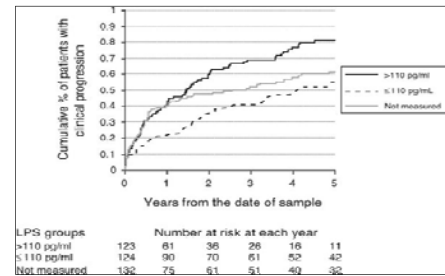
Disruption of GALT is Associated with HIV Disease Progression

- Leaky epithelial barrier caused by HIV
- Antigens enter systemic circulation
- Cytokine release
- Immune activation
- Cells more susceptible to HIV infection

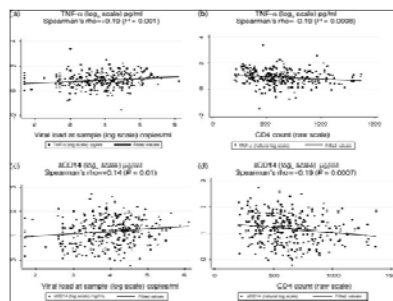
HIV Infection and the Intestinal Mucosal Barrier Microbial Translocation – Immune Activation



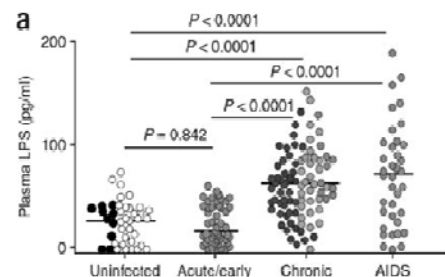
Microbial Translocation Predicts Disease Progression of HIV+ ARV-naïve Patients with High CD4+ Cell Count



Markers of Immune Activation and Microbial Translocation Correlate Positively with Viral Load and Negatively with CD4 Counts



Plasma LPS by HIV Clinical Stage

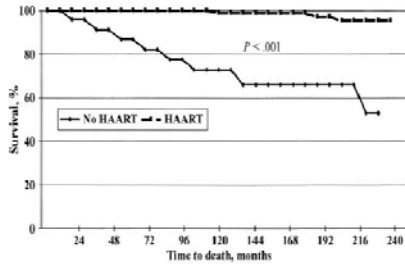


HIV and the GI tract: HAART era

Amazing Transformation in Course of Disease Over 25 Years!

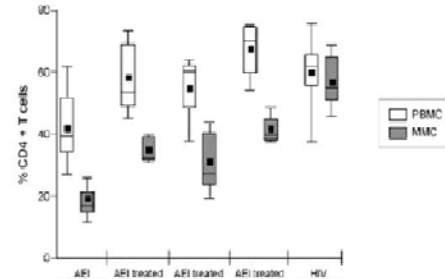


Decreased Mortality Rates in 129 HAART-Treated Children in Southern California



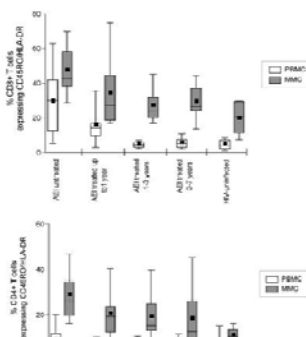
Viani, et al. Clinical Infectious Disease, 2004

Recovery of CD4 Counts with ARV Therapy: Blood versus Colonic Recovery



Mehandru, PLoS Medicine, 2006

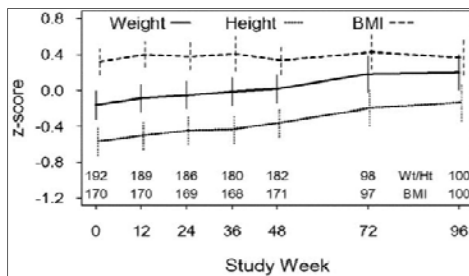
Activated and Proliferating T Cells Remain Elevated with Therapy: Blood versus Colon



Mehandru, PLoS Medicine, 2006

Clinical Consequences Associated With GI tract-Associated Immune Activation

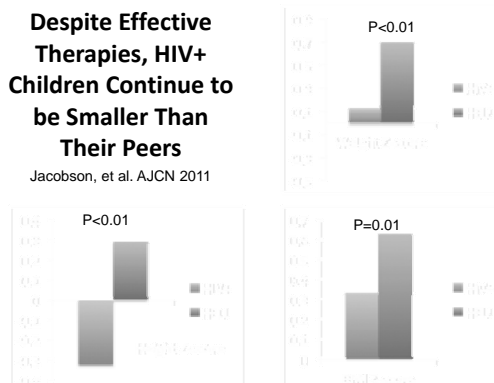
Growth of Human Immunodeficiency Virus-Infected Children Receiving Highly Active Antiretroviral Therapy (PACTG 377)



Nachman S, et al. Pediatric Infectious Disease Journal. 24(4):352-357, April 2005.

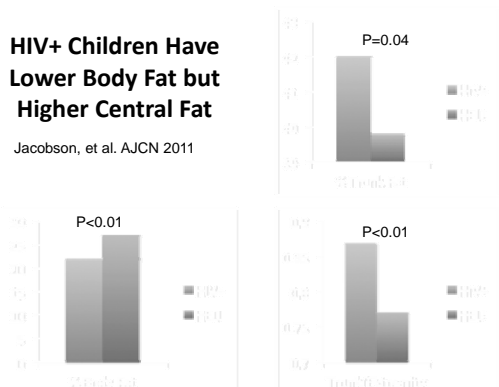
Despite Effective Therapies, HIV+ Children Continue to be Smaller Than Their Peers

Jacobson, et al. AJCN 2011

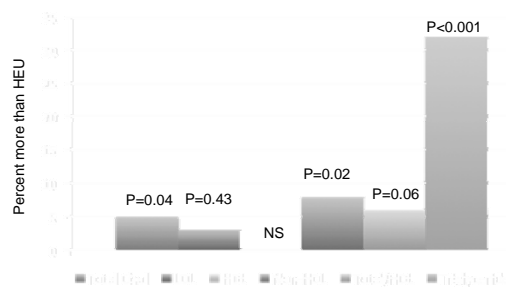


HIV+ Children Have Lower Body Fat but Higher Central Fat

Jacobson, et al. AJCN 2011



Percent Increase in Lipids Compared to HEU



Miller, TL 2012 HIV Medicine

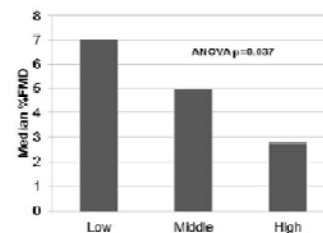
Biomarkers of Vascular Dysfunction*

Log-transformed biomarker	Adjusted Geometric Mean [95% CI]		P-Value
	Control (55)	HIV (105)	
Inflammation			
CRP	0.54 (0.34, 0.86)	0.92 (0.64, 1.34)	0.08
IL-6	0.88 (0.68, 1.14)	1.26 (1.06, 1.51)	0.029
MCP-1	106 (92, 123)	154 (139, 171)	<0.001
Coagulant dysfunction			
Fibrinogen	324 (299, 350)	376 (356, 399)	0.006
P-selectin	28.5 (25, 32.5)	30.9 (28.2, 33.8)	0.29
Endothelial dysfunction			
siCAM	185 (154, 222)	240 (210, 271)	0.032
sVCAM	685 (589, 793)	1141 (1026, 1263)	<0.001
E-selectin	25 (21.6, 29)	29.7 (26.7, 32.7)	0.07
Metabolic dysfunction			
Leptin	6.6 (5.2, 8.2)	5.3 (4.5, 6.2)	0.12

*Means and p-values are adjusted for correlation between siblings, sex, race, age and BMI z-scores. Data were analyzed on the log scale.

Miller TL, et al JAIDS 2010

Median % flow mediated dilation by tertile of plasma lipopolysaccharide levels among ART treated subjects



Blodgett 2012 PLoS One

Adjusted Resting Energy Expenditure by HIV Status*

Variable	HIV-infected (n=110)	Non-HIV infected (n=45)	p Values
Resting Energy Expenditure—estimated mean (SE)			
Kcal/day	1444 (29.6)	1461 (42.3)	0.73
Kcal/kg/day	27.7 (0.6)	26.4 (0.9)	0.15
Kcal/kg-LBM/day	0.83 (0.04)	0.88 (0.07)	0.56
% Predicted kcal/day	98.3 (1.2)	94.3 (1.2)	0.08

Analyses adjusted for age, sex, race

*Watkins R, Miller TL, et al. Abstract presented at the Pediatric HIV Workshop, July 20-21, 2012; Washington DC

Multivariate Model for Predictors of REE Adjusted for Lean Body Mass in 110 HIV+ Children

Variable	Estimate	SE	P-Value
Ethnicity, NHB	0.01	0.07	0.86
Age (yrs)	-0.06	0.01	<0.0001
Sex, female	0.32	0.07	<0.0001
Viral load, log	-0.03	0.03	0.30
IL-6, pg/mL	0.01	0.003	0.003
ICAM, ng/mL	0.001	0.0003	0.002
Leptin, ng/mL	-0.02	0.003	<0.0001

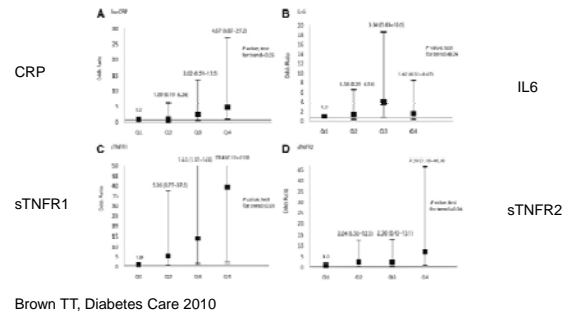
•R² = 0.66

•Other variables considered: CD4%, HAART medications, fibrinogen, MCP-1, E Selectin, P Selectin, VCAM

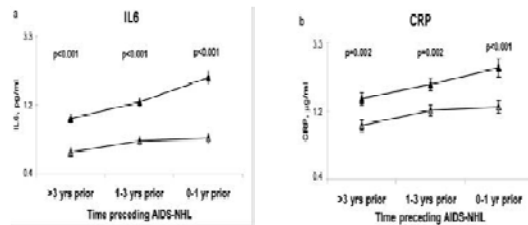
Insulin Resistance and Diabetes in Perinatal HIV

- No published reports of diabetes in HIV infected children/adolescents
- Beregszaszi et al. JAIDS 2005 – 13.2% (17/130) (France)
- Rosso et al. Eur J Endocrinol 2007 – 52% (26/48) (Italy)
- PHACS Cohort – 14% (41/294) (Geffner, et al Pediatr Res 2009)

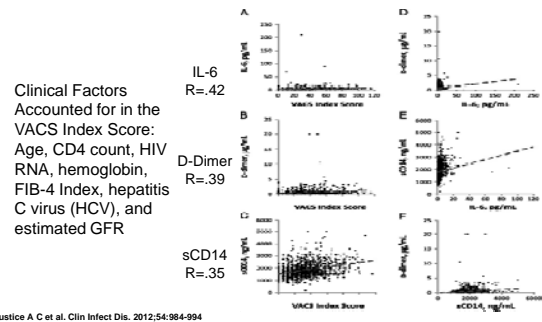
Incidence of Diabetes is Associated with Increased Biomarkers of Inflammation



Markers of Immune Activation are Consistently Elevated >3 years Preceding AIDS-Associated Lymphoma



Biomarkers of Inflammation are Associated with Composite HIV-Specific Aging and Mortality Score in the Veterans Aging Cohort Study (VACS)



Future Therapies

Can ARVs Be Useful in Decreasing Immune Activation Enough to be Therapeutic?

