Dalle malattie opportunistiche alla infiammazione e alle co-morbidità non infettive:
le nuove sfide cliniche di una malattia che cambia
Lo slittamento dei paradigmi...
Le tre ere:
pre-HAART  early-HAART  late-HAART

Malattie opportunistiche  Tossicità acuta da farmaci  Tossicità cronica da farmaci
Pneumocystis Pneumonia --- Los Angeles
In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.”
What's AIDS?

THE WHITE HOUSE

Office of the Press Secretary

PRESS BRIEFING
BY
LARRY SPEAKES

October 15, 1982

The Briefing Room

12:45 P.M. EDT

Q  Larry, does the President have any reaction to the announcement -- the Center for Disease Control in Atlanta, that AIDS is now an epidemic and have over 600 cases?

MR. SPEAKES: What's AIDS?

Q  Over a third of them have died. It's known as "gay plague." (Laughter.)

No, it is. I mean it's a pretty serious thing that one in every three people that get this have died. And I wondered if the President is aware of it?

MR. SPEAKES: I don't have it. Do you? (Laughter.)
Incidenza di AIDS e mortalità: USA 1985-1999

Adattata da: U.S. Centers for Disease Control and Prevention, 2000
Casi di AIDS per milione in alcuni paesi dell’ovest europeo, 1984-1999

Anno diagnosi

Portogallo
Spagna
Italia
Francia
Regno Unito
Germania
“We must make people everywhere understand that the AIDS crisis is not about a few foreign countries, far away. This is a threat to an entire generation; this is a threat to an entire civilization....”

United Nations Secretary-General
Kofi Annan, 2000
Uno sforzo di collaborazione scientifica internazionale senza precedenti nella storia della medicina
Terapia antiretrovirale di Combinazione
Incidenza di AIDS e morte per AIDS in Europa: 1994-2000

Adattata da: EuroSIDA 2000
Le tre ere:

pre-HAART  early-HAART  late-HAART

Malattie opportunistiche  Tossicità acuta da farmaci  Tossicità cronica da farmaci
<table>
<thead>
<tr>
<th>NNRTIs: adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delavirdine</td>
</tr>
<tr>
<td><strong>Rash,</strong></td>
</tr>
<tr>
<td><strong>Headache,</strong></td>
</tr>
<tr>
<td><strong>Increased transaminase levels</strong></td>
</tr>
<tr>
<td>Efavirenz</td>
</tr>
<tr>
<td><strong>Rash,</strong></td>
</tr>
<tr>
<td><strong>CNS symptoms,</strong></td>
</tr>
<tr>
<td><strong>Increased transaminase levels,</strong></td>
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<tr>
<td><strong>False-positive cannabinoid test</strong></td>
</tr>
<tr>
<td>Nevirapine</td>
</tr>
<tr>
<td><strong>Rash,</strong></td>
</tr>
<tr>
<td><strong>Hepatitis including hepatic necrosis</strong></td>
</tr>
</tbody>
</table>

DHHS guidelines 10/11/2003
## NRTIs: adverse events

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Hypersensitivity reactions which can be fatal</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Pancreatitis, Peripheral neuropathy, Nausea, diarrhea, Lactic acidosis</td>
</tr>
<tr>
<td></td>
<td>with hepatic steatosis</td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>Pancreatitis, Peripheral neuropathy, Stomatitis</td>
</tr>
<tr>
<td></td>
<td>Lactic acidosis with hepatic steatosis</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Minimal toxicity, Lactic acidosis with hepatic steatosis</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Minimal toxicity, Lactic acidosis with hepatic steatosis</td>
</tr>
</tbody>
</table>

DHHS guidelines 10/11/2003
<table>
<thead>
<tr>
<th>NRTIs: adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tenofovir</strong></td>
</tr>
<tr>
<td>Asthenia, headache</td>
</tr>
<tr>
<td>Diarrhea, nausea, vomiting and flatulence</td>
</tr>
<tr>
<td>Rare reports of renal insufficiency</td>
</tr>
<tr>
<td><strong>Zidovudine</strong></td>
</tr>
<tr>
<td>Bone marrow suppression</td>
</tr>
<tr>
<td>GI intolerance</td>
</tr>
<tr>
<td>Headache, insomnia, asthenia</td>
</tr>
<tr>
<td><strong>Lactic acidosis with hepatic steatosis</strong></td>
</tr>
<tr>
<td><strong>Stavudine</strong></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Lipodistrophy</td>
</tr>
<tr>
<td>Rapidly ascending neuromuscular weakness (rare)</td>
</tr>
<tr>
<td><strong>Lactic acidosis with hepatic steatosis</strong></td>
</tr>
</tbody>
</table>

DHHS guidelines 10/11/2003
<table>
<thead>
<tr>
<th>PIs: adverse events</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amprenavir</strong></td>
<td>GI intolerance, nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
</tr>
<tr>
<td></td>
<td>Oral paresthesias</td>
</tr>
<tr>
<td></td>
<td>Transaminase elevation</td>
</tr>
<tr>
<td></td>
<td>Fat redistribution, lipid abnormalities and hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>Possible increased bleeding in pts with hemophilia</td>
</tr>
<tr>
<td><strong>Atazanavir</strong></td>
<td>Indirect hyperbilirubinemia</td>
</tr>
<tr>
<td></td>
<td>Prolong PR interval-1st degree AV block</td>
</tr>
<tr>
<td></td>
<td>Fat redistribution, lipid abnormalities and hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>Possible increased bleeding in pts with hemophilia</td>
</tr>
<tr>
<td><strong>Indinavir</strong></td>
<td>Nephrolithiasis</td>
</tr>
<tr>
<td></td>
<td>Indirect hyperbilirubinemia</td>
</tr>
<tr>
<td></td>
<td>Fat redistribution, lipid abnormalities and hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>Possible increased bleeding in pts with hemophilia</td>
</tr>
<tr>
<td><strong>PIs: adverse events</strong></td>
<td></td>
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<tr>
<td>------------------------</td>
<td></td>
</tr>
</tbody>
</table>
| **Lopinavir/rit**      | GI intolerance, nausea, vomiting, diarrhea  
|                        | Asthenia, transaminase elevation  
|                        | Fat redistribution, lipid abnormalities and hyperglycemia  
|                        | Possible increased bleeding in pts with hemophilia |
| **Nelfinavir**         | Diarrhea  
|                        | Transaminase elevation  
|                        | Fat redistribution, lipid abnormalities and hyperglycemia  
|                        | Possible increased bleeding in pts with hemophilia |
| **Ritonavir**          | GI intolerance, nausea, vomiting, diarrhea, taste perversion  
|                        | Asthenia, paresthesias (circumoral and extremities), pancreatitis, hepatitis  
|                        | Elevated CPK, uric acid  
|                        | Fat redistribution, lipid abnormalities and hyperglycemia  
|                        | Possible increased bleeding in pts with hemophilia |
PIs: adverse events

**Saquinavir**

GI intolerance, nausea, vomiting, diarrhea
Abdominal pain and dyspepsia (soft gel capsules)
Headache
Transaminase elevation
Fat redistribution, lipid abnormalities and hyperglycemia
Possible increased bleeding in pts with hemophilia
### Blak Box warnings: NRTIs

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Symptoms and Actions</th>
</tr>
</thead>
</table>
| Abacavir     | **Fatal hypersensitivity reactions reported:**
|              | - Fever, skin rash, fatigue, GI and respiratory symptoms.  
|              | Abc should be discontinued as soon as hypersensitivity reaction is suspected.  
|              | Abc should not be restarted. If restarted, more severe symptoms will recur within hours and might include life-threatening hypotension and death.  
|              | **Lactic acidosis with hepatic steatosis including fatal cases.** |
| Didanosine   | **Fatal and nonfatal pancreatitis**
|              | - DDI should be withheld if pancreatitis is suspected.  
|              | - DDI should be discontinued if pancreatitis is confirmed.  
|              | **Fatal lactic acidosis among pregnant women** who received DDI+d4T.  
|              | - DDI+d4T should only be used during pregnancy if the potential benefit clearly outweighs the potential risks.  
|              | **Lactic acidosis with hepatic steatosis including fatal cases.** |
| Emtricitabine| **Lactic acidosis with hepatic steatosis including fatal cases.** |
| Lamivudine   | **Lactic acidosis with hepatic steatosis including fatal cases.** |
|              | Patients with HIV infection should receive only dosage and formulations appropriate for treatment of HIV (use Epivir-EBV only to treat chronic hepatitis B). |
### Blak Box warnings: NRTIs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Common Adverse Effects</th>
</tr>
</thead>
</table>
| **Zalcitabine** | - Severe peripheral neuropathy
                              use with caution among patients with pre-existing neuropathy
                              - In rare cases DDC can cause pancreaticitis, therapy should withheld until pancreatitis is excluded
                              - Rare cases of hepatic failure and death among patients with HBV infection
                              - Lactic acidosis with hepatic steatosis including fatal cases |
| **Stavudine**     | - Lactic acidosis with hepatic steatosis including fatal cases
                              - Fatal lactic acidosis among pregnant women who received DDI+d4T
                              DDI+d4T should only be used during pregnancy if the potential benefit clearly outweighs the potential risks
                              - Fatal and nonfatal pancreaticitis when d4T was part of a combination regimen with DDI with or without hydroxyurea |
| **Zidovudine**    | - Hematologic toxicities, including granulocytopenia and severe anemia among advanced HIV patients
                              - Prolonged use has been associated with symptomatic myopathy
                              - Lactic acidosis with hepatic steatosis including fatal cases |
## Blak Box warnings: NNRTIs

| Nevirapine         | - Severe life-threatening hepatotoxicity  
|                   | - Severe life-threatening and even fatal skin reactions |

## Blak Box warnings: PIs

| Amprenavir         | - Potential risk of toxicity for substantial amounts of the excipient propylene glycol in oral solution |
|                   | - Possible effect of the drug on hepatic metabolism of certain non-sedating antihistamines, sedative hypnotics, antiarrhythmics or ergot alkaloids |
| Ritonavir          | - Possible effect of the drug on hepatic metabolism of certain non-sedating antihistamines, sedative hypnotics, antiarrhythmics or ergot alkaloids |
Il mitocondrio

- Fonte energetica della cellula
- Essenziale per la normale funzionalità della cellula
- Ha DNA proprio, separato da quello della cellula
- Il DNA mitocondriale viene replicato con mtDNA polimerasi diversa (polimerasi gamma)
Tossicità mitocondriale

Meccanismo

- Replicazione DNA mitocondriale catalizzato da DNA polimerasi gamma
- Analoghi nuclos(t)idici inibiscono questa polimerasi
- Alterazione generazione energia mitocondriale

Adattato da Brinkman, AIDS 1998
tossicità mitocondriale

NRTIs
alterazione del mtDNA
trascrizione di enzimi abnormi
fosforilazione ossidativa difettiva
neuropatie
acidosi lattica
miopatie
pancreatiti
Chronic liver disease
Cognitive disorders
Non-AIDS cancers
Chronic renal disease
Depression
Osteoporosis
CVD
Diabetes mellitus
Frailty
CVD
frailty:

Infirmity: the state of being weak in health or body

(especially from old age)
Co-morbidità = Tossicità cronica da farmaci

Un’equazione accettabile?
L’infettivologo è farmacocentrico!
Emergence of Non-AIDS Comorbidities

- Chronic HIV Infection
- ART Toxicity
- HCV and other Co-infections
- Insulin Resistance
- Dyslipidemia
- Inflammation & Fibrosis
- Decreased Physical Functioning
- Aging
- Genetics
- Obesity, Exercise, Diet, Smoking

END ORGAN DISEASE

Warriner AH et al. ID Clin N Am. 2014
Le tre ere:
pre-HAART    early-HAART    late-HAART

Malattie opportunistiche  Tossicità acuta da farmaci  Tossicità cronica da farmaci  Co-morbidità
L'infiammazione entra in gioco
Causes or promotes most, if not all, all age-related diseases, including cancer
...Over the past decade, it has become widely accepted that inflammation is a driving force behind chronic diseases that will kill nearly all of us. (Cancer. Diabetes and obesity. Alzheimer’s disease. Atherosclerosis.) Here, inflammation wears a grim mask, shedding its redeeming features and making sick people sicker...

...The surest way to prove that inflammation is driving any disease is by blocking it and testing whether that helps...

...Mediating inflammation in chronic diseases is a new frontier, its success still uncertain...
l’endotelio ha un peso complessivo di 1,5 kg circa e copre un’area di 600 m²
Figure 1. The healthy endothelium not only mediates endothelium-dependent vasodilation, but also actively suppresses thrombosis, vascular inflammation, and hypertrophy. Nitric oxide is a particularly important mediator of both endothelium-dependent vasodilation and anti-inflammatory and antithrombotic effects of the endothelium, and endothelium-dependent vasomotion is therefore thought to represent a “read-out” of other important functions of the endothelium.
Bonetti O. et al.
Arterioscler Thromb Vasc Biol. 2003; 23: 168-175
Prevalent study

1998-2019
Precocious lesions of the carotid vessels in HIV-1 infected patients treated with protease inhibitors


- 13 pts treated with PI:
- 4 pts with pathologic carotid IMT
- 1 pt with carotid plaques
- 1 pr with congenital lesion (kinking)

Premature lesions of the carotid vessels in HIV-1-infected patients treated with protease inhibitors
“Premature vascular lesions in HIV-positive patients: a clockwork bomb that will explode?”
AIDS 2004, 18:1023-1028

Maggi P, Lillo A, Perilli F, Maserati R, Chirianni A

on behalf of the PREVALEAT group.

Colour-doppler ultrasonography of carotid vessels in patients treated with antiretroviral therapy: a comparative study
“…These findings were alarming, and a flurry of research reports and editorials created a sense of impending “epidemic” of cardiovascular disease, described by one writer as a “clockwork bomb” that might explode”.

James H. Stein
(Cardiovascular risks of antiretroviral therapy. - Editorial)
## Results /2

### Comparison of ultrasonographic findings

<table>
<thead>
<tr>
<th></th>
<th>PI 105</th>
<th>NNRTI 125</th>
<th>2NRTI/Naïve 63</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acquired lesions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMT</td>
<td>25</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>IMT+plaques</td>
<td>24</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>plaques</td>
<td>6</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total plaques</strong></td>
<td>30 (28.5 %)</td>
<td>9 (7.2%)</td>
<td>6 (9.5%)</td>
</tr>
<tr>
<td><strong>Normal findings</strong></td>
<td>50 (47.6 %)</td>
<td>106 (84.8 %)</td>
<td>54 (85.7 %)</td>
</tr>
<tr>
<td><strong>Median IMT value (mm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>right carotids</td>
<td>1.2 (1.01-2.47)</td>
<td>1.31 (1.01-2.33)</td>
<td>1.24 (1.02-1.4)</td>
</tr>
<tr>
<td>left carotids</td>
<td>1.3 (1.01-3.0)</td>
<td>1.36 (1.01-2.08)</td>
<td>1.4 (1.1-3.5)</td>
</tr>
<tr>
<td><strong>Percentage of stenosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>right carotids</td>
<td>42.9% (15-54)</td>
<td>35% (25-66)</td>
<td>30% (20-40)</td>
</tr>
<tr>
<td>left carotids</td>
<td>41.9% (15-70)</td>
<td>38% (25-52)</td>
<td>46.7 (one patient)</td>
</tr>
</tbody>
</table>
Data Collection on Adverse events of Anti-HIV Drugs

DAD Study

- Prospective multinational cohort study initiated in 1999 (Europe, USA, Australia)
- 11 cohorts; 188 clinics; 21 countries
- 23468 patients
- 36145 person years of follow up
The DAD study group. Class of antiretroviral drugs and the risk of myocardial infarction.

Atherosclerotic stenosis

Eur J Vasc Endovasc Surg. 2005; 29:167-170
Eur J Vasc Endovasc Surg. 2005; 29:167-170

Surgical experience with carotid stenosis in young HIV-1 positive patients under antiretroviral therapy: an emerging problem?
Iso-hypoechogenic lesion

- No cleavage plain
- Smooth surface
- Homogeneous aspect

HIV + patients
Hyperechogenic lesion
Dishomogeneous aspect (shadow cones)
Irregular surface
Cleavage plain

HIV-negative, atheromasic patients
The GI tract as a site of HIV pathogenesis

Brenchley et al. Nat Med 2006

Sandler & Douek, Nat Reviews 2012
How is HIV Unique?
Look to your guts!
Chronic treated HIV: a state of unresolved inflammation
Come ridurre l'infiammazione residua?
Residual inflammatory risk: what are options after statin treatment?
Reducing inflammation lowers CV events and also cancer incidence/mortality

Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial

Paul M Ridker, Jean G MacFadyen, Tom Thuren, Brendan M Everett, Peter Libby, Robert J Glynn, on behalf of the CANTOS Trial Group

Ridker P et al Lancet August 27, 2017
Targeting inflammation: Moving upstream
IL-1β; INHIBITION SIGNIFICANTLY REDUCES ATHEROSCLEROTIC INFLAMMATION IN TREATED HIV

Priscilla Hsue
University of California, San Francisco, CA, USA
IL-1β inhibition using canakinumab

• Canakinumab is a human monoclonal IL-1β antibody indicated for treatment inflammatory disorders such as CAPS and Muckle-Wells syndrome
  – Dosing is quarterly subcutaneous injection
• Binds IL-1β and blocks interaction of cytokines with type I and II receptors
• Produces a rapid and sustained inhibition of inflammation with only minimal effects on lipids
Conclusions

- In this pilot study (n=10), a single dose of canakinumab was well-tolerated in treated HIV-infected individuals.
- Canakinumab significantly reduced inflammatory markers (IL-6, hsCRP, and sCD163).
- A single dose of canakinumab did not impact T cell activation or monocyte phenotypes (with exception of CCR5+ monocytes).
- Monocyte function was reduced which is consistent with inflammatory marker findings.
- Canakinumab significantly reduced arterial inflammation and bone marrow activity.
Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

CANTOS study

- 10,061 pts with previous MI AND hsCRP ≥2mg/l
- Primary end point: non fatal MI, non fatal stroke, or CV death

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1</td>
<td>(ref)</td>
<td>(ref)</td>
</tr>
<tr>
<td>On-treatment hsCRP ≥ 2.0 mg/L</td>
<td>0.91</td>
<td>(0.81-1.03)</td>
<td>0.14</td>
</tr>
<tr>
<td>On-treatment hsCRP &lt; 2.0 mg/L</td>
<td>0.74</td>
<td>(0.65-0.83)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Cumulative incidence over follow-up (years)

Ridker, Lancet 2018

COSTO ELEVATO ($200.000/anno)
ALTO TASSO DI INFEZIONI FATALI
Impact of Low Dose Methotrexate on Immune Activation and Endothelial Function in Treated HIV

CROI Conference, Boston, MA 2018

A5314 Study Team:

Priscilla Y. Hsue, Heather J. Ribaudo, Steven G. Deeks, Tanvir Bell, Carl Fichtenbaum, Eric Daar, Diane Havlir, Eunice Yeh, Ahmed Tawakol, Michael Lederman, Judith S. Currier, and James H. Stein
A5314 Design: randomized, double-blind, placebo-controlled clinical trial

HIV-infected individuals ≥ 40 years old who have been virologically suppressed and on continuous ART for > 24 with CD4+ > 400 cells/mm³ and have documented CVD or an 1 risk factor

Randomize (with stratification by current statin use)

Arm 1
LDMTX (5 mg MTX once a week) + folic acid (1 mg/day)
Study entry through Week 1 visit
通过Week 12 visit
通过Week 24 visit

Arm 2
Placebo (5 mg once a week) + folic acid (1 mg/day)
通过Week 12 visit
通过Week 24 visit

Week 36 (final visit)

*MTX, placebo are all discontinued at week 24; folic acid continued until week 28
LDMTX associated with a modest reduction in CD4+ T-cell count

LDMTX associated with a modest decrease in CD4+ T-cell count at week 24 only (median -58, IQR -163, +47, p=0.016) which resolved by week 36
LDMTX associated with a significant decrease in CD8+ T-cells

LDMTX associated with significant decrease in CD8+ T-cells at weeks 8, 12, and 24 which resolved by week 36
No change in endothelial function as assessed by FMD (%)

AD population: Change in Brachial Artery FMD (%)

No change in secondary endpoints including brachial artery diameter and hyperemic flow velocity
No change in inflammatory/coagulation biomarkers

IL-6 increased over time in both groups:
Increase at week 4 and remained higher in the placebo group (BL to week 24 p=0.037); not significant in the LDMTX arm (p=0.15)
No difference between the two groups at any time point

No difference in the change between groups for hsCRP, IP-10, sCD163, D-dimer fibrinogen or VCAM
LDMTX had a modest impact on CD4+ T cell activation

AD: Absolute Change in (CD3+CD4+) CD38+HLADR+

Difference between treatment groups modestly different at week 4, p=0.05 and significant at week 24, p=0.007
Arterial inflammation was assessed using FDG PET/CT imaging at 0 and 24 weeks, and measured as standardized uptake values (SUV).

LDMTX may reduce arterial inflammation in HIV-infected adults with or at risk for ASCVD, at least as measured by ΔSUV. This finding may explain the apparent beneficial impact of LDMTX on ASCVD risk in chronic inflammatory diseases. The potential effect of LDMTX on arterial inflammation in HIV should be studied in a larger cohort.
LDMTX reduced arterial inflammation in HIV

- Subset (N=28) of individuals from 5314 underwent FDG-PET/CT at 0 and 24 weeks
- LDMTX reduced arterial SUV vs. PBO (change in SUV: -0.034 [-0.311, 0.095] vs. 0.096 [-0.081, 0.313], p=0.05).
- Changes in cycling CD8+ T cells correlated with changes in SUV.

Tawakol A et al Abstract 684 LB
Simple and scalable: ASA?

121 participants
ASA 100mg or 300mg or placebo for 12 weeks
O’Brien et al. Open Forum Infect Dis. 2017
Visbiome ES was safe and well tolerated among this cohort. No significant effect of Visbiome ES on systemic inflammatory markers was identified. While high loss to follow up in the placebo arm limits the strength of our conclusions, these results do not support Visbiome ES as a viable strategy to reduce systemic inflammation in suppressed PWH with preserved CD4 counts.
FACTOR X INHIBITION REDUCES COAGULATION BUT NOT INFLAMMATION IN PERSONS WITH HIV

Jason V. Baker

The oral direct factor Xa inhibitor edoxaban substantially reduced coagulation activity among persons with HIV receiving ART with viral suppression. In this study, no effect on soluble systemic inflammatory markers was observed and there was an increased risk for minor bruising and bleeding events.
| **TABLE 1:** | Receiving Edoxaban ('E', n=40) | Receiving Placebo ('P', n=41) |  
| **Biomarkers** | **Pre-Treatment, Mean (SD)** | **Change, Mean (SD)** | **Pre-Treatment, Mean (SD)** | **Change, Mean (SD)** | **p-value**  
| **IL-6 (pg/mL)** | 0.69 (0.36) | 0.10 (0.29) | 0.83 (0.61) | -0.04 (0.55) | 0.26  
| **IL-1β (pg/mL)** | 0.04 (0.02) | 0.01 (0.03) | 0.04 (0.02) | 0.01 (0.03) | 0.34  
| **sTNFR-1 (pg/mL)** | 1369 (248) | -15 (201) | 1377 (299) | -8 (173) | 0.57  
| **sCD163 (ng/mL)** | 686 (243) | -3 (108) | 685 (240) | -5 (106) | 0.81  
| **TAT (µg/L)** | 12.1 (20.0) | -7.9 (18.2) | 9.0 (14.7) | -3.5 (15.3) | <0.001  
| **D-dimer (µg/mL)** | 0.21 (0.13) | -0.06 (0.12) | 0.22 (0.16) | -0.03 (0.13) | 0.002  
| **INR** | 1.06 (0.09) | 0.11 (0.11) | 1.05 (0.08) | 0.02 (0.06) | <0.001  
| **Hemoglobin (g/dL)** | 14.70 (1.42) | -0.15 (0.65) | 14.29 (1.56) | 0.19 (0.70) | 0.05  
| **Platelets (10^3/µL)** | 238.1 (58.0) | -1.93 (26.1) | 238.9 (54.9) | 4.9 (24.7) | 0.18  

*p-value* is for comparison of change on Edoxaban versus change on Placebo considering all follow-up measures during the 4-month study drug period, controlled for assigned treatment sequence and pre-treatment biomarker level; **Comparison of change analyzed on natural log scale, but mean biomarker levels presented as untransformed values in table; TNFR-1 = tumor necrosis factor receptor-1; TAT = thrombin anti-thrombin complex; INR = international normalized ratio for prothrombin time*
Simple and scalable: Statins

Plaque Regression with Atorvastatin

SCD14 Declines with Rosuvastatin

Funderburg, JADS, 2015, Toribio M et al. AIDS 2017
In a highly selected cohort of HIV-positive adults on suppressive ART, RUX was safe and well tolerated but did not significantly reduce IL6 levels. On RUX treatment there was a modest decrease in sCD14 with an increase in circulating T cells through mechanisms undefined. This proof-of-concept trial provides a rationale for future studies of Jak inhibitors in PLWH who have residual inflammation or immune dysfunction despite long-term suppressive ART.

* Janus kinase (JAK) family of enzymes for signal transduction. Drugs that inhibit the activity of these Janus kinases block cytokine signalling.
Grazie 😊