Immune Activation and HIV Persistence: *New Therapeutic Approaches*

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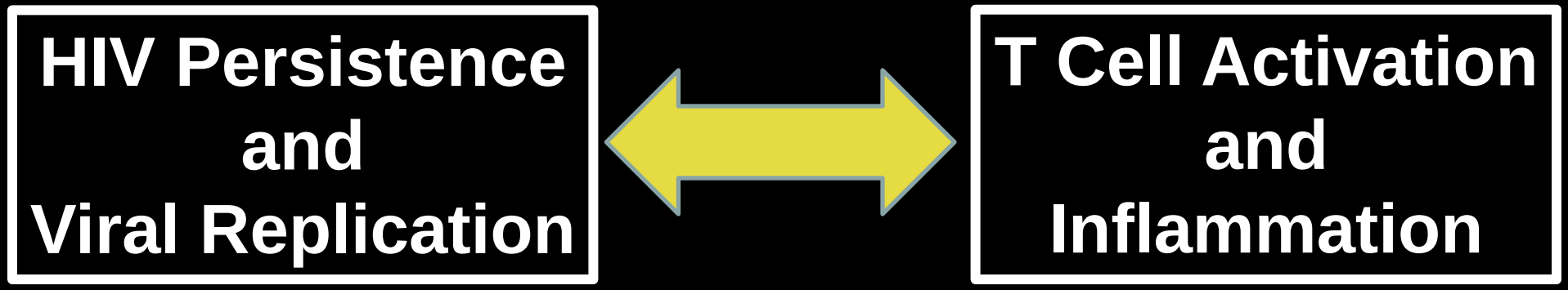
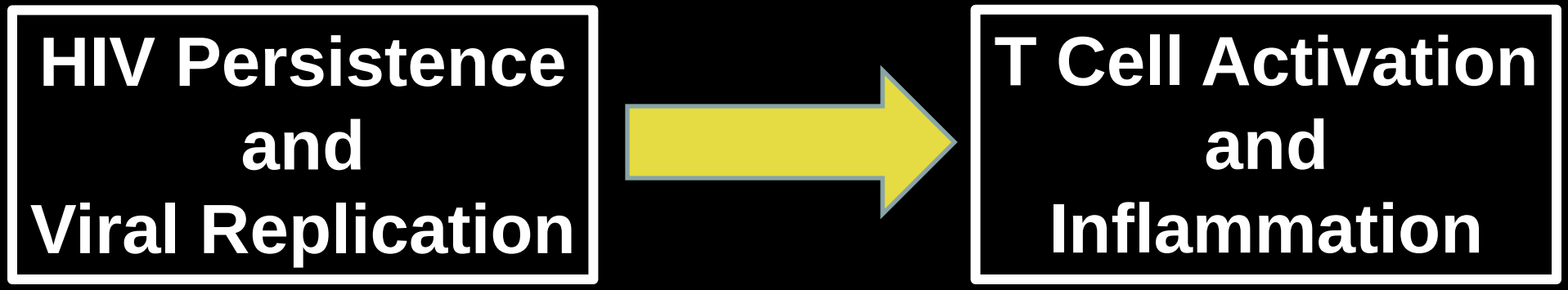
Which is Cause vs. Effect?



Viral Persistence



If viral persistence causes inflammation, strategies to decrease viral production/replication should reduce inflammation

Although intensification does not affect plasma viremia, it does alter episomal DNA levels (2-LTR circles), suggesting replication is occuring at low levels

nature medicine

HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects

Maria J Buzón[1,9], Marta Massanella[1,9], Josep M Llibre[2], Anna Esteve[3], Viktor Dahl[4], Maria C Puertas[1], Josep M Gatell[5], Pere Domingo[6], Roger Paredes[1,2], Mark Sharkey[7], Sarah Palmer[4], Mario Stevenson[7], Bonaventura Clotet[1,2], Julià Blanco[1] & Javier Martinez-Picado[1,8]

Effect of raltegravir-containing intensification on HIV burden and T-cell activation in multiple gut sites of HIV-positive adults on suppressive antiretroviral therapy

Steven A. Yukl[a], Amandeep K. Shergill[a], Kenneth McQuaid[a], Sara Gianella[b], Harry Lampiris[a], C. Bradley Hare[c], Mark Pandori[d], Elizabeth Sinclair[c], Huldrych F. Günthard[b], Marek Fischer[b], Joseph K. Wong[a] and Diane V. Havlir[c]

Increase in 2–Long Terminal Repeat Circles and Decrease in D-dimer After Raltegravir Intensification in Patients With Treated HIV Infection: A Randomized, Placebo-Controlled Trial

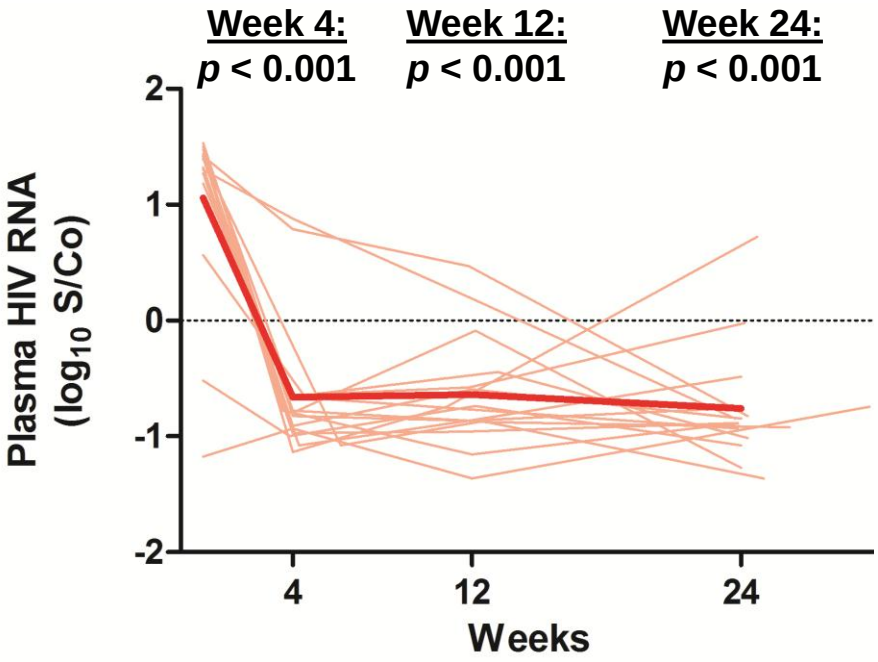
Hiroyu Hatano,[1] Matthew C. Strain,[4,5] Rebecca Scherzer,[1,3] Peter Bacchetti,[2] Deborah Wentworth,[6] Rebecca Hoh,[1] Jeffrey N. Martin,[2] Joseph M. McCune,[1] James D. Neaton,[6] Russell P. Tracy,[7] Priscilla Y. Hsue,[1] Douglas D. Richman,[4,5] and Steven G. Deeks[1]

PI Effect?

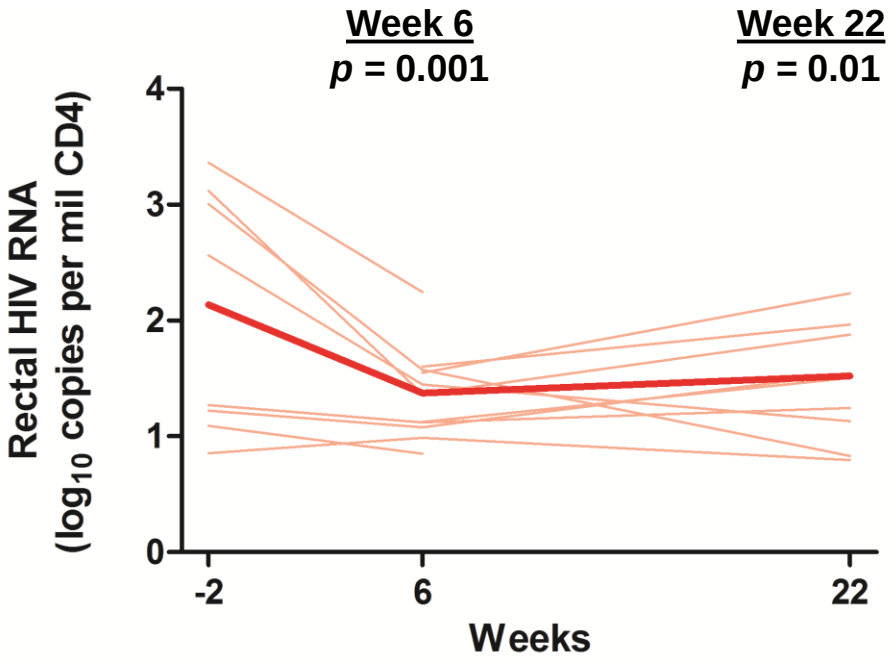
- **Increase in 2-LTR circles more likely to occur in subjects taking PI-based ART** (Buzon, Nat Med ’10; Hatano, JID ‘13)
- **In ART-suppressed subjects with CD4<350, no effect of RGV intensification on SCA**
  - **Significant decrease in ultrasensitive plasma RNA in subset of subjects taking PI-based ART** (Hatano, JID ‘11)
- **Residual viral replication may be occurring in anatomic compartments that are less accessible to PI’s** (Fletcher, CROI ‘12)
- **For PI’s with a shorter half-life and steep dose response curve, new infection events may be occurring when drug concentrations are low** (Shen, Nat Med ‘08; Jilek, Nat Med ‘12)

Controllers had Significant Decrease in RNA with ART

Plasma RNA



Rectal RNA



Decrease in Rectal RNA at Week 22:

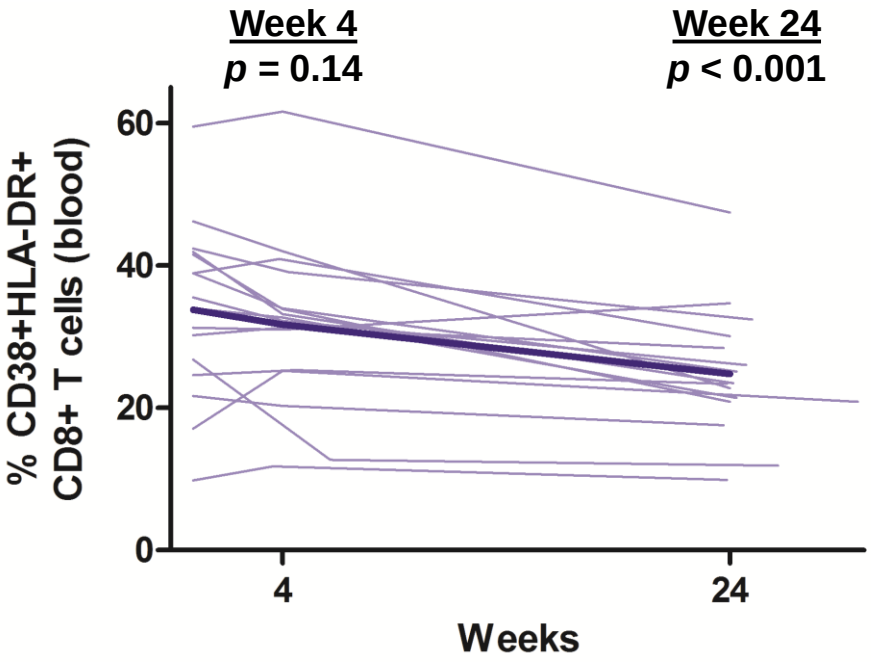
Rectal RNA: - 0.61 $\log_{10}$ copies/mil CD4+ (p = 0.01)

** P-values refer to change from baseline at each timepoint*

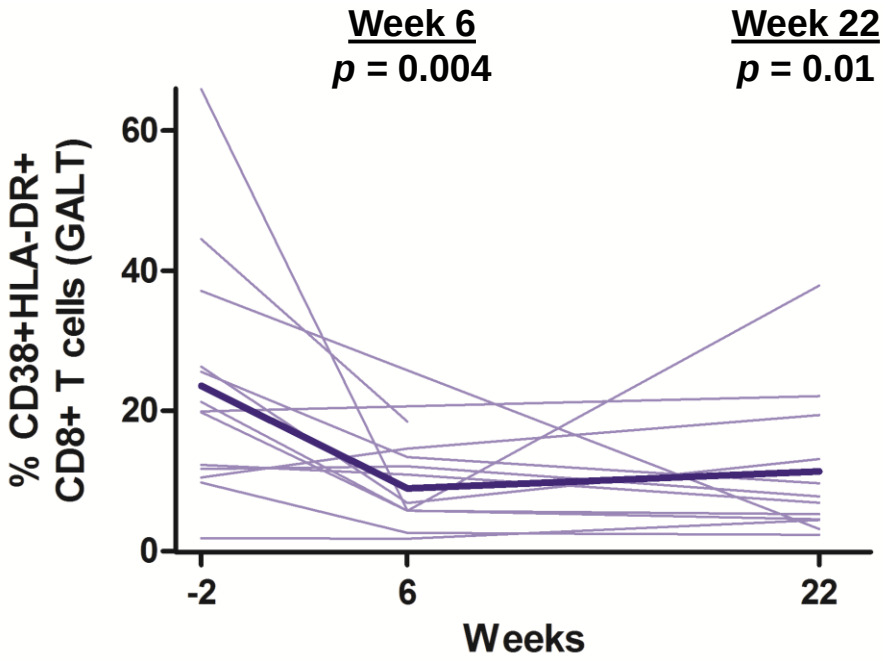
Hatano et al, PLoS Path 2013

Controllers had Significant Decrease in Immune Activation with ART

CD8 (blood)



CD8 (GALT)



Decrease in T cell activation at Week 24/22:

CD8 activation (blood): - 9.0 % ($p < 0.001$)
CD8 activation (GALT): - 12.2% ($p = 0.01$)

**** P-values refer to change from baseline at each timepoint***

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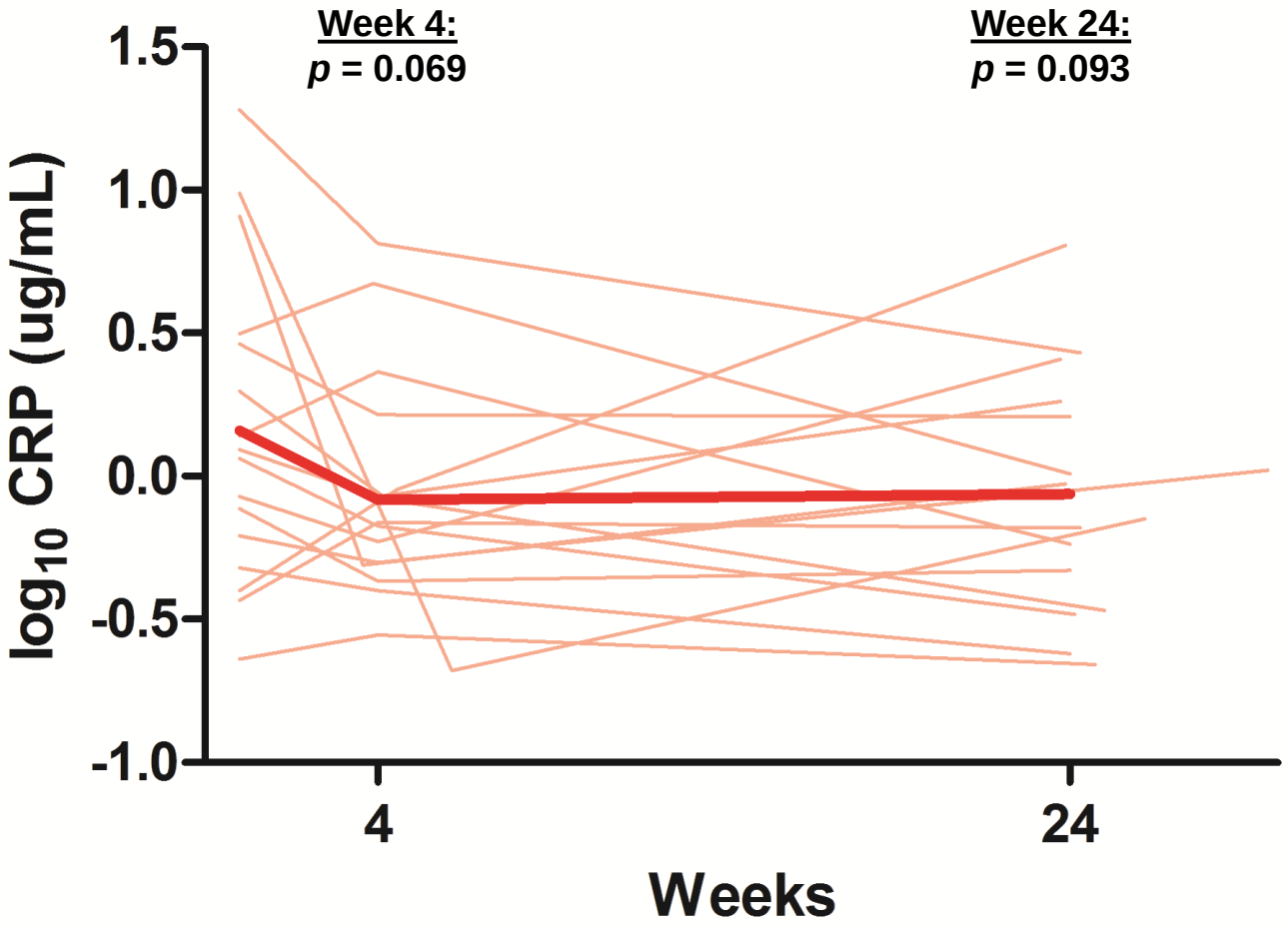
Controllers had Trend Towards Decrease in C-Reactive Protein with ART



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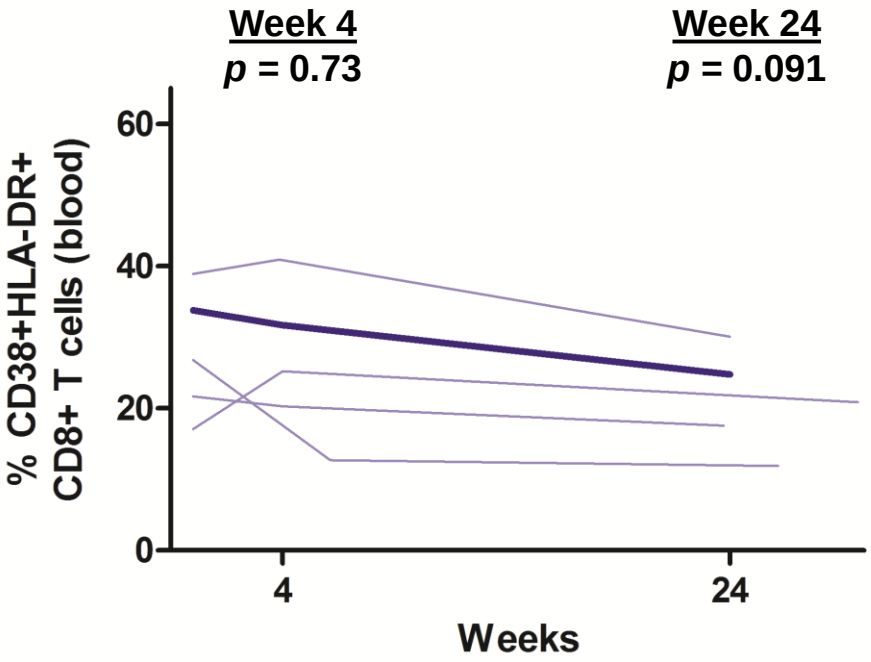
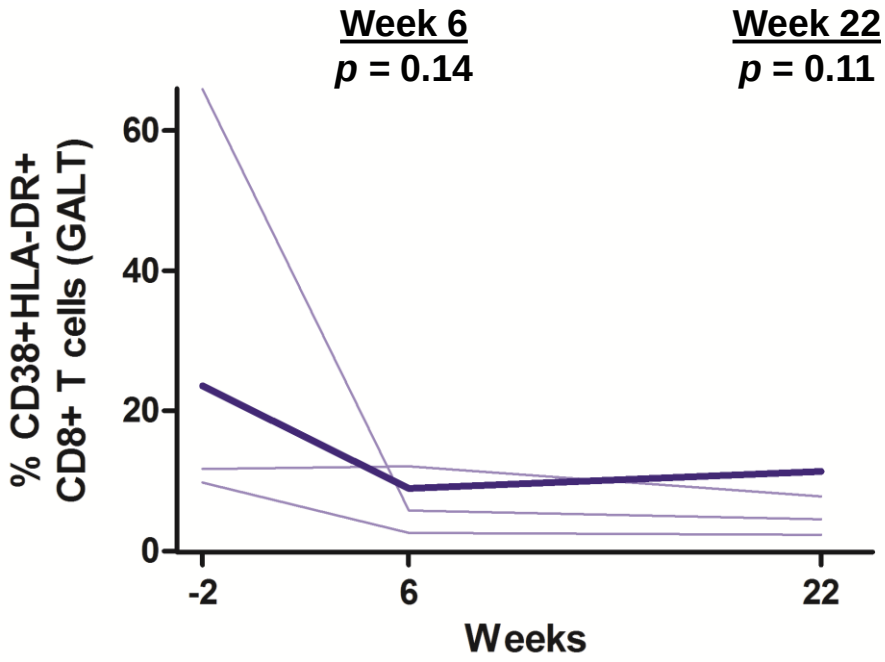
Hatano et al, PLoS Path 2013

"Elite" Controllers had Trend Towards Decrease in Immune Activation with ART

CD8 (Blood)



CD8 (GALT)



Decrease in T cell activation at Week 24/22:

CD8 activation (blood): - 6.0 % (*p* = 0.091)
CD8 activation (GALT): - 24.0 % (*p* = 0.11)

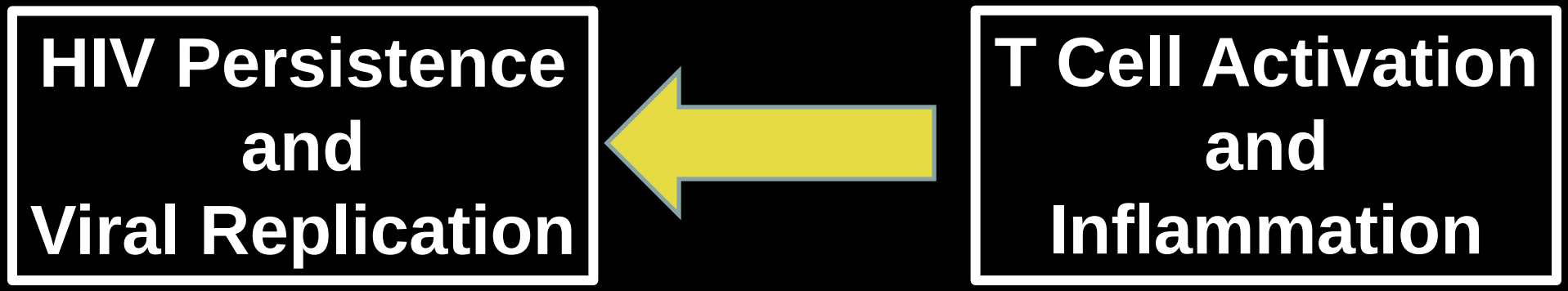
**** P-values refer to change from baseline at each timepoint***

Hatano et al, PLoS Path 2013

Maximal Suppression of HIV Replication

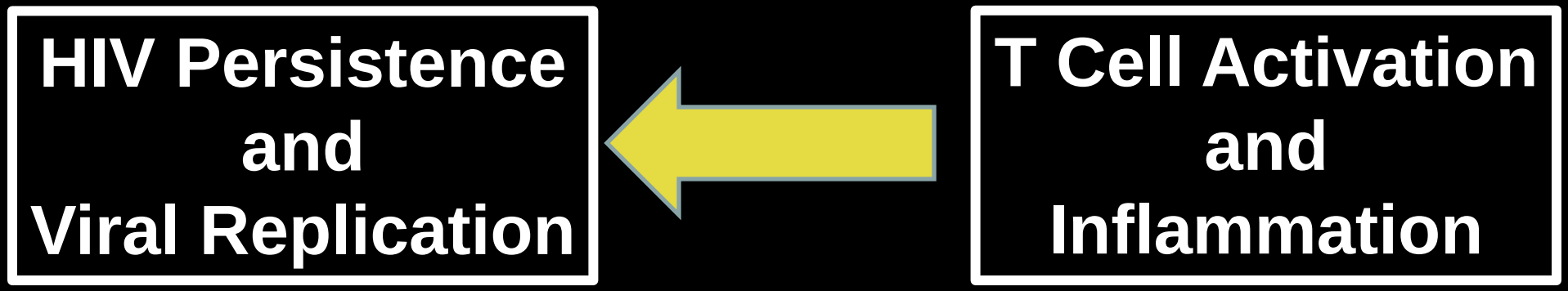
- **Effective, highly bioavailable ARVs that have robust lymphoid tissue penetration** (Fletcher, CROI ‘12)
- **Initiation of ARVs as early as possible during acute infection** (Jain, JID ‘13; Saez-Cirion, PLoS Path ’13; Ananworanich, CROI ’13; Persaud, NEJM ‘13)

Inflammation



- More virus production
- More target cells
- Homeostatic proliferation
- Upregulation of negative regulators (PD-1)
- Poor clearance mechanisms

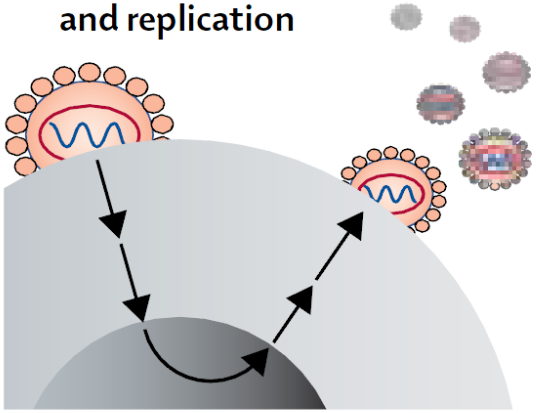
Inflammation



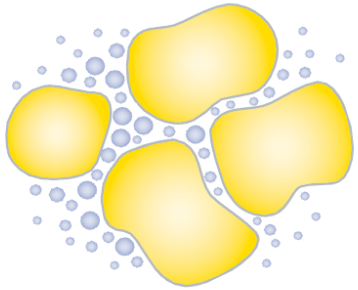
If inflammation causes persistence, anti-inflammatory approaches may accelerate cure

Multiple Factors Cause Persistent Inflammation During ART

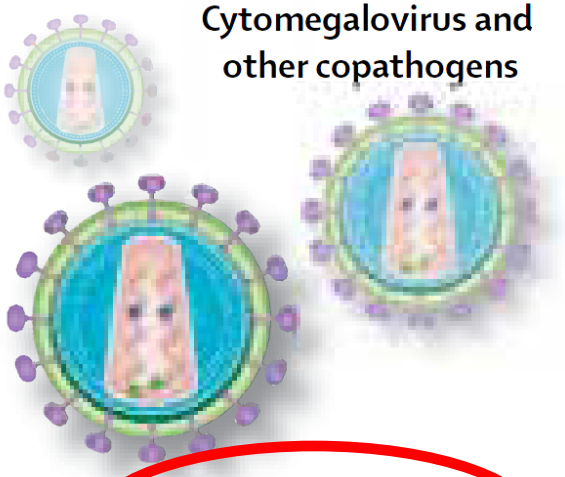
HIV production and replication



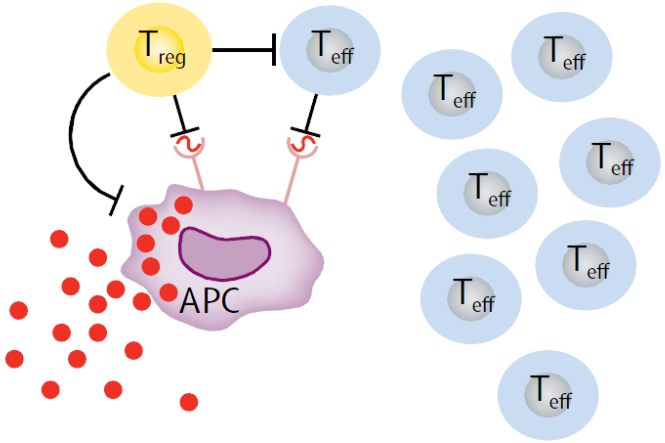
ART toxicity, lipodystrophy, and traditional risk factors



Cytomegalovirus and other copathogens

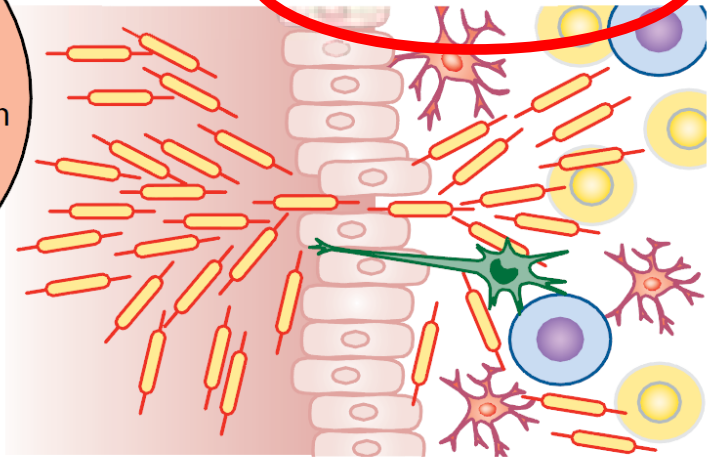


Loss of regulatory cells



Inflammation
↑Monocyte activation
↑T-cell activation
↑Endothelium adhesion
Dyslipidaemia
Hypercoagulation

Microbial translocation



Comorbidities
(cardiovascular disease, cancer, kidney disease, liver disease, osteopenia/osteoporosis, neurocognitive disease)

Deeks, Lewin, Havlir; Lancet 2013

Potential Interventions to Decrease Microbial Translocation

- **Rifaximin (ACTG 5286)**
  - **Minimally absorbed oral antibiotic that is concentrated in GI tract and has broad spectrum bactericidal activity**
- **Sevelamer (ACTG 5296)**
  - **Oral phosphate binder that binds bacterial endotoxin in GI tract**

Prebiotics and Probiotics

- **Overrepresentation of pathogenic bacteria and underrepresentation of beneficial bacteria in HIV infection** (Gori, JCM ’08; Cunningham-Rundles, Nutrients ‘11)
- **Gut “dysbiosis” associated with mucosal immune disruption, T cell activation, and chronic inflammation in treated HIV-infected individuals** (Vujkovic-Cvijin, Sci Transl Med ‘13)
- **RCT in *untreated* HIV-infected individuals, prebiotic x12 weeks improved gut microbiota composition and decreased sCD14** (Gori, Mucosal Immunol ‘11)

Prebiotic and Probiotic Supplementation in Treated SIV

Probiotic/prebiotic supplementation of antiretrovirals improves gastrointestinal immunity in SIV-infected macaques

Nichole R. Klatt,[1] Lauren A. Canary,[1] Xiaoyong Sun,[2] Carol L. Vinton,[1] Nicholas T. Funderburg,[3] David R. Morcock,[4] Mariam Quiñones,[1] Clayton B. Deming,[5] Molly Perkins,[1] Daria J. Hazuda,[6] Michael D. Miller,[7] Michael M. Lederman,[3] Julie A. Segre,[5] Jeffrey D. Lifson,[4] Elias K. Haddad,[2] Jacob D. Estes,[4] and Jason M. Brenchley[1]

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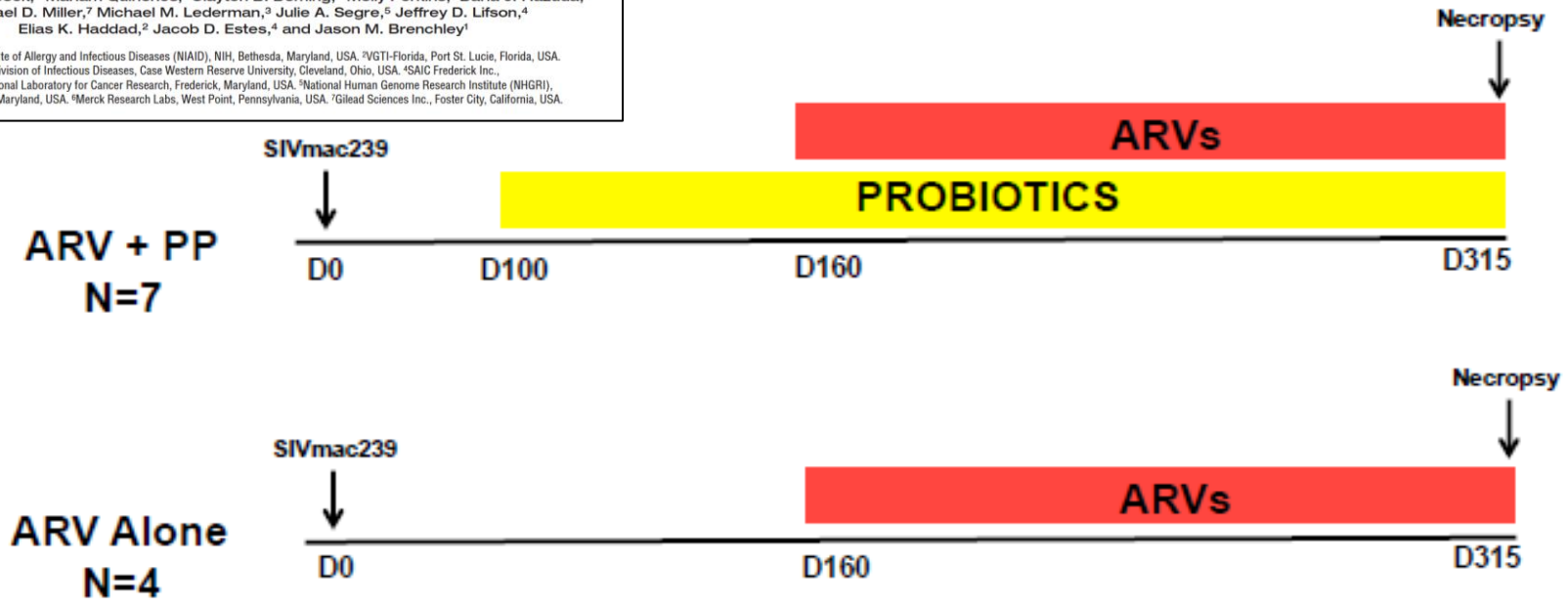


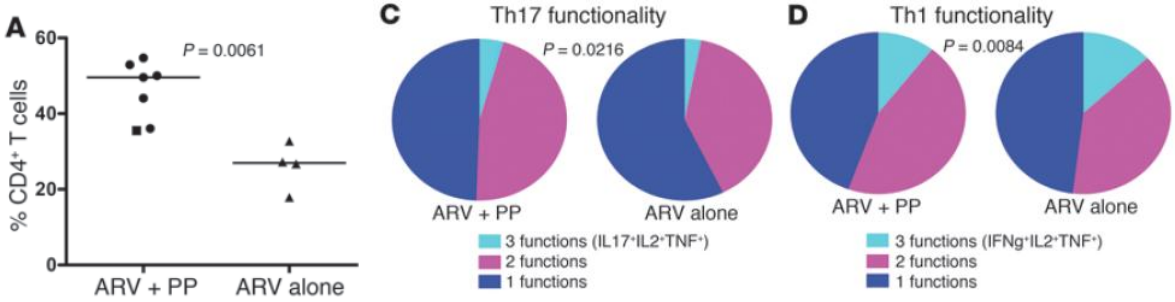
•ARVs = RTIs: PMPA, FTC & INIs: L'812, L'564

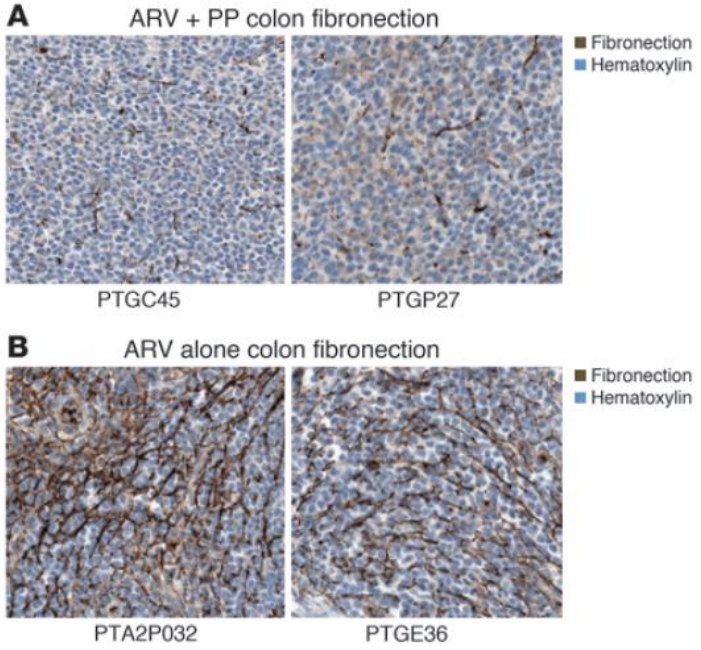
•Probiotics = VSL#3 (*Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus bulgaricus Streptococcus thermophilus*)
& Culturelle (*Lactobacillus GG* & prebiotics)

Klatt et al, JCI 2013

Prebiotic and Probiotic Supplementation in Treated SIV

- Increased colonic CD4 reconstitution
- Increased frequency/functionality of APCs in colon
- Decreased lymphoid fibrosis in the colon





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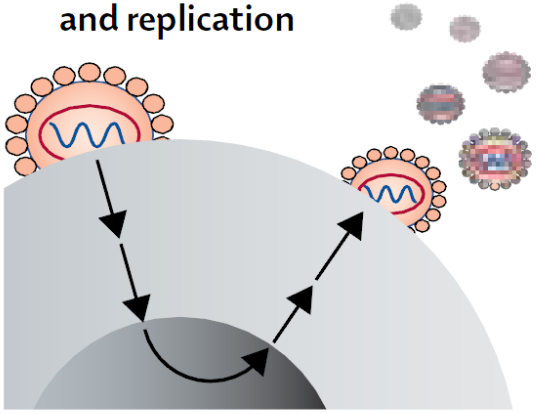

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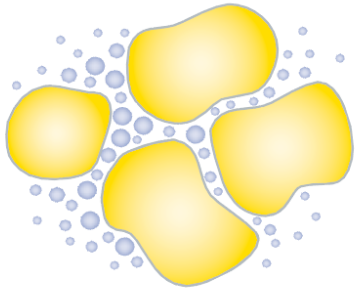

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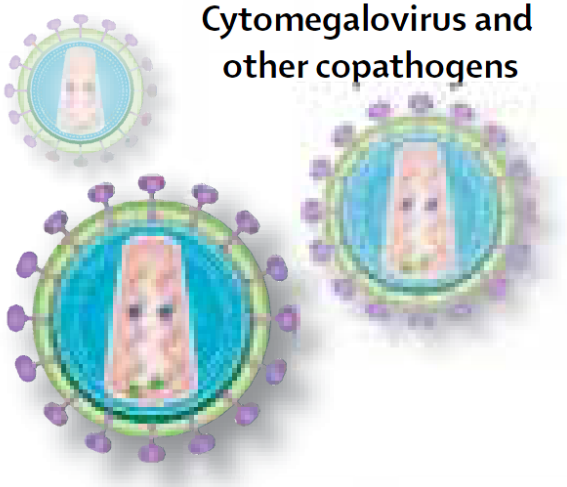

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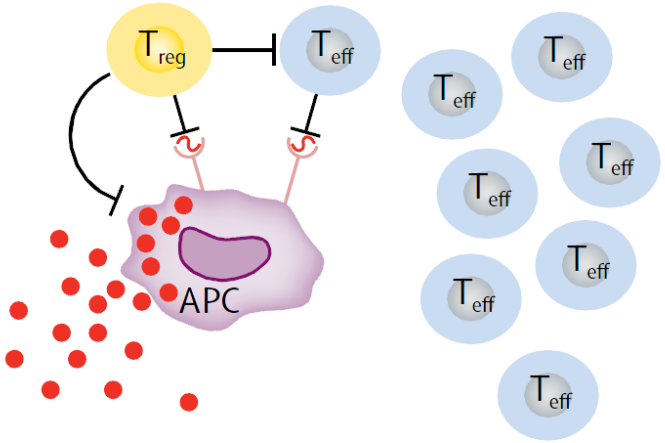

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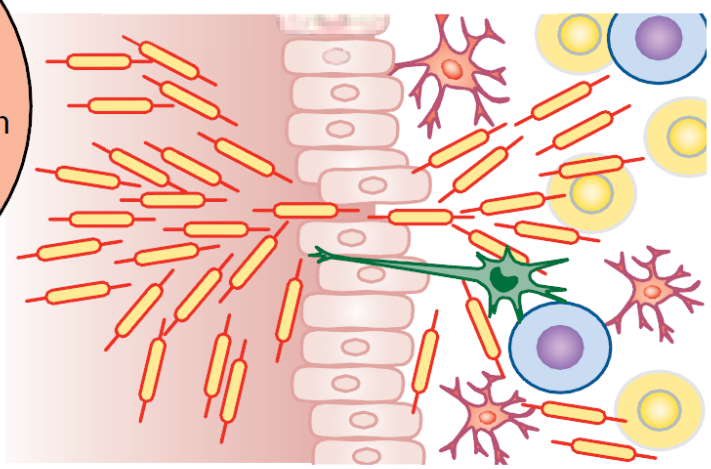

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Deeks, Lewin, Havlir; Lancet 2013

Blockade of Type I Interferon Signaling may be Beneficial in Chronic HIV Infection

Persistent LCMV Infection Is Controlled by Blockade of Type I Interferon Signaling

John R. Teijaro,[1]* Cherie Ng,[1]* Andrew M. Lee,[1]† Brian M. Sullivan,[1] Kathleen C. F. Sheehan,[2] Megan Welch,[1] Robert D. Schreiber,[2] Juan Carlos de la Torre,[1] Michael B. A. Oldstone[1]‡

Blockade of Chronic Type I Interferon Signaling to Control Persistent LCMV Infection

Elizabeth B. Wilson,[1] Douglas H. Yamada,[1] Heidi Elsaesser,[1] Jonathan Herskovitz,[1] Jane Deng,[2] Genhong Cheng,[1] Bruce J. Aronow,[3] Christopher L. Karp,[4]* David G. Brooks[1]†

- **IFN-alpha has antiviral effects in untreated HIV**
- **LCMV infection**
  - **Acute infection: IFN-alpha has antiviral effects**
  - **Chronic infection: chronic and persistent signaling by IFN-alpha leads to potent immunomodulatory effects that prevent adaptive immune responses (eg, through expression of PD-1) and promote viral persistence**
  - **Blockade of IFN-alpha led to decreased immune activation, decreased PD-1 expression, restored lymphoid architecture, and enhanced viral clearance**

Therapeutic Options in Development

- Anti-inflammatory drugs
  - Chloroquine, hydroxychloroquine
  - NSAIDs (aspirin, mesalamine, COX-2 inhibitors)
  - Statins
  - Minocycline
  - Methotrexate
  - Lenalidomide
  - Biologics (IL-6 inhibitors, anti-INFa)
- Anti-coagulants: low dose warfarin, aspirin, clopidogrel
- Anti-infective therapy: CMV, HCV/HBV, HSV, EBV
- Microbial translocation: rifaximin, sevelamer, prebiotics/probiotics, colostrum
- Anti-fibrotic drugs: ACE inhibitors, ARBs
- Enhance T cell renewal: IL-7
- Anti-aging: sirolimus caloric restriction, omega-3 fatty acids, diet, exercise
- Chemokine receptor inhibitors: maraviroc

Multiple mechanisms account for HIV persistence, many of which are being addressed therapeutically

Acknowledgements

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