Integrase inhibitors and inflammatory process

Jean-Pierre Routy M.D. FRCPC
McGill Health centre

Vancouver
May 25, 2013
HIV, 30 years ago
HIV: Today challenges

• Management:
  – Test, treat, retain in care with best ART
  – Aging
  – Inflammation and non-AIDS events

• Research:
  – Vaccine
  – Eradication
  – Social stigma
To achieve a reduction in HIV transmission, HAART programs must ensure the effectiveness and quality of a cascade of services from testing and referral to care to ensuring ongoing adherence to HAART. Large US cohorts have found that women, IVDU, younger and non-white patients were less likely to achieve virologic suppression, and may require targeted outreach along the cascade of care.

*US ≤200 copies/mL, BC and France < 50 copies/mL

1. Adapted from CDC, MMWR 2011;60:1618-1623
2. Adapted from Nosyk B, et al. CROI 2013; Atlanta, GA. #1029
3. Costagliola D, et al. ibid. #1030
4. Althoff K, et al. ibid. #1026
5. Novak R, et al. ibid. #1032a
6. Horberg M, et al. ibid. #1033
HIV inflammation and comorbidity
Inflammation and chronic diseases: A commun pathway

B Chronic inflammatory disease

Primary pathophysiology

DAMP

Low-grade inflammatory response

Persistent stimulus

Macrophage/lymphocyte recruitment

Amplification of inflammatory response
Tissue damage

Normal tissue

Neutrophil
Monocyte
M1 macrophage
M2 macrophage
Tissue debris

Tebas & Glass Science Jan 2013
Inflammation pathway in HIV inflammation

Lewin S CROI 2013
Inflammation markers and mortality

<table>
<thead>
<tr>
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<th>SMART/ESPRIT</th>
<th>FRAM</th>
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<th>UARTO</th>
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Lewin S CROI 2013
Inflammation markers and non-AIDS events

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<tr>
<td>D-dimer</td>
<td>✔</td>
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</table>

References:

Time to non-AIDS events and death association with IL-6 and D-dimers

N= 3766, control arms of the SMART, ESPRIT and SILCAAT trials, all on ART
Mean CD4=500cells/ul; mean follow up for 5 years

CROI 2013
CD16+ monocytes independently predict progression of coronary artery calcium++

- **n=436; SUN cohort; longitudinal study of coronary artery calcium (CAC) over 2 years**
- **CD16+ monocytes are “inflammatory”**
- **Predict risk of CAC progression**

**Table:**

<table>
<thead>
<tr>
<th>Monocyte Phenotype</th>
<th>OR (95% CI) for CAC Progression*</th>
<th>p-value</th>
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<tbody>
<tr>
<td>CD14+/CD16+</td>
<td>1.65 (1.08, 2.52)</td>
<td>0.02</td>
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<tr>
<td>CD14var/CD16+</td>
<td>1.69 (1.12, 2.54)</td>
<td>0.01</td>
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<tr>
<td>CD14-/CD16+</td>
<td>1.36 (0.98, 1.88)</td>
<td>0.06</td>
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</table>

*no association with T-cell activation markers

Baker et al., 20th CROI 2013 abstract #68LB
MECHANISMS OF DISEASE

Mechanisms of Acute Coronary Syndromes and Their Implications for Therapy

Peter Libby, M.D.

INFLAMMATION, COLLAGEN METABOLISM, AND PLAQUE RUPTURE AND THROMBOSIS

N ENGL J MED 368;21  NEJM.ORG  MAY 23, 2013
Macrophages and atherosclerosis

- Macrophages and atherosclerosis lesions and thrombi
- Overproduction of 3 matrix-metalloproteinase (MMP) interstitial collagenases:
  - MMP-1, MMP-8, and MMP-13
Inflammation predisposing coronary arteries to rupture and thrombosis
Contribution of classes of ART on HIV-related inflammation?

- **NRTIs:**
  - Mitochondrial toxicity

- **NNRTI:**
  - Mild lipid effect (sustiva)

- **PIs:**
  - Lipid changes, ritonavir

- **Integrase inhibitors:**
  - Not well defined
### Integrase inhibitors

**Table 1** Major characteristics of the 3 INSTIs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RAL</th>
<th>EVG/cobi</th>
<th>DTG</th>
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</thead>
<tbody>
<tr>
<td><strong>Dosing</strong></td>
<td>400 mg bid</td>
<td>150/150 mg qd</td>
<td>50 mg qd in INSTI-naive and 50 mg bid in INSTI-experienced patients</td>
</tr>
<tr>
<td><strong>STR</strong></td>
<td>No</td>
<td>Yes (TDF/FTC/EVG/cobi)</td>
<td>Together with abacavir(ABC) and 3TC</td>
</tr>
<tr>
<td>To be taken with food</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>In vitro activity</strong></td>
<td>33 nM (IC₉₅)</td>
<td>45 ng/mL (IC₉₅)</td>
<td>0.064 μg/mL (0.15 μM) (IC₉₀)</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>83%</td>
<td>98 %</td>
<td>99.3%</td>
</tr>
<tr>
<td><strong>Terminal half-life</strong></td>
<td>9 h</td>
<td>12.9 h/3.5 h</td>
<td>15 h</td>
</tr>
<tr>
<td><strong>Drug-drug interactions</strong></td>
<td>with inducers of UGT1A1 (rifampin)</td>
<td>Presence of a strong CYP3A inhibitor such as cobicistat creates the potential for an increase in systemic exposure of CYP3A substrates</td>
<td>with inducers of UGT1A1 (rifampin)</td>
</tr>
<tr>
<td>Interaction with proton pump inhibitors and antacids</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Mutations</strong></td>
<td>E92Q</td>
<td>T66I/A/K</td>
<td>H51Y</td>
</tr>
<tr>
<td></td>
<td>Y143C/H/R</td>
<td>E92Q/G</td>
<td>R263K</td>
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<tr>
<td></td>
<td>Q148 H/K/R</td>
<td>T97A</td>
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Mesplede et al Retrovirol 2013
Proportion (%) of Patients Achieving HIV RNA <50 (95% CI) Over Time

**Final 5-Year Double-Blind Results From STARTMRK**

![Graph showing the proportion of patients achieving HIV RNA levels <50 copies/mL over time.](image)

- **Raltegravir 400 mg bid.**
  - Weeks: 0, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240
  - Percentages: 86, 82, 81, 79, 75, 69, 76, 67, 71%
  - Number of contributing patients: 281, 278, 279, 280, 281, 277, 280, 281, 281, 277, 279

- **Efavirenz 600 mg qHS.**
  - Weeks: 0, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240
  - Percentages: 82, 79, 75, 69, 67, 61%
  - Number of contributing patients: 282, 282, 282, 281, 282, 282, 282, 282, 282, 279

Non-Completer = Failure Approach
Change From Baseline in CD4 Over Time

Final 5-Year Double-Blind Results
From STARTMRK

Number of Contributing Patients

- Raltegravir 400 mg bid. 281272266 258 255 250 240 235 231 235 227 222
- Efavirenz 600 mg qHS. 281268266 251 252 243 234 228 224 220 218 212
Étude randomisée de phase III en double aveugle

Patients prétraités, naïfs d’INI
CV > 400 copies/ml*
Randomisation 1:1
stratification selon la CV initiale (≤ ou > 50 000),
l’administration de DRV/r et de molécules pleinement actives

Phase randomisée

DTG 50 mg x 1/j
+ RAL PBO + BR

RAL 400 mg x 2/j
+ DTG PBO + BR

Randomisation

Analyse intermédiaire planifiée

S24

S48

* À l’inclusion et un 2e test consécutif > 400 copies/ml dans les 4 mois précédant l’inclusion (si CV à l’inclusion > 1 000 copies/ml, pas d’indication à un 2e test).
PBO : placebo ; BR : traitement associé.
Résultats (1) : pourcentage de patients avec CV < 50 copies/ml à S24 (Snapshot, ITTm)

DTG 50 mg x 1/j est statistiquement supérieur à RAL 400 mg x 2/j à S24

Différence de réponse ajustée à S24 (IC$_{95}$) :
+ 9,7 en faveur de DTG (3,1 % - 15,9 %) ; p = 0,003

→ Efficacité immunologique comparable : + 99 (DTG) vs + 93 (RAL) cellules/mm$^3$
Study 102

Efficacy Endpoint: HIV-1 RNA <50 c/mL

Virologic success (HIV-1 RNA <50 c/mL) as defined by FDA Snapshot algorithm

1. Zolopa A, et al. CROI 2013; Atlanta, GA. #553
Integrated Study 102 and 103 - Week 96

Change from Baseline in CD4 Cells

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Week</th>
<th>Change in CD4 (cells/mm³), Mean (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>EVG/COBI/FTC/TDF</td>
<td></td>
<td>+275</td>
</tr>
<tr>
<td>FTC/TDF (n=)</td>
<td></td>
<td>701 686 673 660 654 653 659 653 630</td>
</tr>
<tr>
<td>EFV/FTC/TDF</td>
<td></td>
<td>+223</td>
</tr>
<tr>
<td>ATV + RTV + FTC/TDF</td>
<td></td>
<td>+273</td>
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<tr>
<td>(n=)</td>
<td></td>
<td>+261</td>
</tr>
</tbody>
</table>

Zolopa A, et al. CROI 2013; Atlanta, GA. #553
Integrated Study 102 and 103 - Week 96

Change from Baseline in Fasting Lipids

No difference in change in TC:HDL ratio at Week 48 or 96

Zolopa A, et al. CROI 2013; Atlanta, GA. #553
Integrase inhibitor and inflammation

• All associated with:
  – Faster V.L. decay than any PI or NNRTI
  – Higher CD4 recovery on long-term
  – No significant impact on lipid

• Raltegravir and its impact on:
  – Inflammation
  – HIV reservoir
Decrease in Inflammatory and Coagulation Biomarkers in HIV-Infected Patients After Switching from Enfuvirtide to Raltegravir in the Randomized ANRS 138 EASIER Trial

Erika Silva¹, Isabelle Charreau², Bernard Gourmel¹, Samia Mourah¹, Issa Kaidi¹, Brigitte Guillon², Nathalie De Castro¹, François Caron³, Josephine Braun², Jean-Michel Molina¹ and the ANRS Easier study group.

¹AP-HP-Hôpital Saint-Louis, Université Paris 7, PARIS, ²INSERM SC10, VILLEJUF, ³Hôpital Universitaire Charles Nicolle, ROUEN, all in France.

**Figure 1: IL6 levels in log₁₀ (pg/mL)**

- **DS:** Delay Switch
- **IS:** immediate Switch

P = <0.0001

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<th>Week</th>
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<th>IS</th>
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<tr>
<td>0</td>
<td>81</td>
<td>83</td>
</tr>
<tr>
<td>24</td>
<td>78</td>
<td>79</td>
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<tr>
<td>48</td>
<td>75</td>
<td>72</td>
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</table>
A Randomized Trial of Raltegravir Replacement for Protease Inhibitor or Non-Nucleoside Reverse Transcriptase Inhibitor in HIV-Infected Women with Lipohypertrophy

Jordan E. Lake, M.D., M.Sc.,¹ Grace A. McComsey, M.D.,² Todd M. Hulgan, M.D., M.P.H.,³ Christine A. Wanke, M.D.,⁴ Alexandra Mangili, M.D., M.P.H.,⁴ Sharon L. Walmsley, M.D., M.Sc.,⁵ M. Sean Boger, M.D., PharmD,⁶ Ralph R. Turner, Ph.D., M.P.H.,⁷ Heather E. McCreath, Ph.D.,¹ and Judith S. Currier, M.D., M.Sc.¹

well with percent visceral AT change. No RAL-related adverse events occurred. Compared to continued PI or NNRTI, switch to RAL was associated with statistically significant 24-week improvements in total and LDL cholesterol but not AT volumes. Additional insights into AT and metabolic changes in women on RAL will be provided by 48-week follow-up of the immediate-switch arm.

AIDS PATIENT CARE and STDs
Volume 26, Number 9, 2012
Changes in Cardiovascular Biomarkers in Subjects Switching from Ritonavir-Boosted Protease Inhibitors to Raltegravir: The SPIRAL Study.

E Martinez¹, P Monteiro¹, JM Llibre², F Gutierrez³, D Podzamczer⁴, A Antela⁵, J Berenguer⁶, I Perez¹, J Pich¹, JM Gatell¹, and the SPIRAL Study Group.

¹ Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona; ² Germans Trias i Pujol University Hospital and Lluita contra la SIDA Foundation, Badalona; ³ Hospital General Universitario de Elche, Elche; ⁴ Hospital Universitari de Bellvitge, L’Hospitalet de Llobregat; ⁵ Complexo Hospitalario Universitario de Santiago, Santiago de Compostela; and ⁶ Hospital General Universitario Gregorio Marañón, Madrid, all in Spain.
SPIRAL Cardiovascular Biomarkers
Sub-study: Participants

- Stable HIV-infected adults (≥ 18 years)
- PI/r plus ≥ 2 non-PI antiretrovirals
- HIV-RNA < 50c/mL for ≥ 6 months
- No prior RAL use

Patients randomized (n=282)

RAL (n=142)

RL (n=139)

n=3 Excluded (protocol violation) n=3

n=13 Study drug discontinuation before w48 n=14
n=7 Lack of paired samples n=6

RAL (n=119) PI/r (n=114)
Biomarkers and lipids measured at baseline and 48 weeks

Initiation

Inflammation

hsCRP, MCP-1
OPG, IL-6
TNF-alpha, IL-10

Progression

Endothelial dysfunction

Insulin resistance

ICAM-1, VCAM-1
E-Selectin, P-Selectin
Insulin, Adiponectin

Complication

Hypercoagulability

D-dimer

Lipids (fasting)

Triglycerides, Total cholesterol, LDL cholesterol, HDL cholesterol
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<tr>
<th>Characteristic</th>
<th>RAL (n=119)</th>
<th>PI/r (n=114)</th>
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<tr>
<td>Age, years (IQR)</td>
<td>43 (40-49)</td>
<td>44 (40-50)</td>
</tr>
<tr>
<td>Men (n, %)</td>
<td>94 (79)</td>
<td>83 (73)</td>
</tr>
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<td>NRTI backbone at entry (n, %)</td>
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<tr>
<td>3TC/FTC plus TDF</td>
<td>69 (58)</td>
<td>64 (56)</td>
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<td>3TC/FTC plus ABC</td>
<td>24 (20)</td>
<td>23 (20)</td>
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<tr>
<td>3TC/FTC plus AZT</td>
<td>9 (8)</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Other</td>
<td>17 (14)</td>
<td>17 (15)</td>
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<tr>
<td>PI/r at entry (n, %)</td>
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<tr>
<td>LPV/r</td>
<td>52 (44)</td>
<td>54 (47)</td>
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<tr>
<td>ATV/r</td>
<td>45 (38)</td>
<td>40 (35)</td>
</tr>
<tr>
<td>Other</td>
<td>22 (18)</td>
<td>20 (18)</td>
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<tr>
<td>Patients on 1st ART (n, %)</td>
<td>15 (13)</td>
<td>14 (12)</td>
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<tr>
<td>ART exposure, years (median, range)</td>
<td>10 (5-12)</td>
<td>10 (6-12)</td>
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<tr>
<td>PI exposure, months (median, range)</td>
<td>31 (19-45)</td>
<td>30 (17-50)</td>
</tr>
<tr>
<td>Previous suboptimal ART or virological failure (n, %)</td>
<td>68 (55)</td>
<td>55 (48)</td>
</tr>
<tr>
<td>Patients with AIDS (n, %)</td>
<td>43 (36)</td>
<td>42 (37)</td>
</tr>
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</table>
Lipids: Median difference of percent change RAL minus PI/r (95% CI)
Biomarkers: Median difference of percent change RAL minus PI/r (95% CI)
## Correlations between $\Delta$ biomarkers and $\Delta$ lipids

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<tr>
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<th>$\Delta$Triglycerides</th>
<th>$\Delta$Total cholesterol</th>
<th>$\Delta$LDL cholesterol</th>
<th>$\Delta$HDL cholesterol</th>
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<tr>
<td>$\Delta$hsCRP</td>
<td>-</td>
<td>-</td>
<td>Spearman's rho 0.2415 (P=0.0016)</td>
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<tr>
<td>$\Delta$MCP-1</td>
<td>-</td>
<td>Spearman's rho 0.1608 (P=0.0320)</td>
<td>-</td>
<td>Spearman's rho 0.1807 (P=0.0202)</td>
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<tr>
<td>$\Delta$OPG</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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<td>$\Delta$IL-6</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>$\Delta$IL-10</td>
<td>-</td>
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<tr>
<td>$\Delta$TNF-alpha</td>
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<td>$\Delta$ICAM-1</td>
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<td>$\Delta$E-selectin</td>
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<td>$\Delta$P-selectin</td>
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<td>$\Delta$Adiponectin</td>
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<td>$\Delta$Insulin</td>
<td>Spearman's rho 0.2842 (P=0.0001)</td>
<td>Spearman's rho 0.2125 (P=0.0040)</td>
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<td>$\Delta$D-dimer</td>
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</table>

Only correlations showing a P value <0.005 are shown.
HIV reservoirs and Raltegravir

- ART intensification
- ART tissue penetration
- Viral replication
- Long-lived cells
- Inflammation
- Stem cellness
HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects

Maria J Buzón, Marta Massanella, Josep M Llibre, Anna Esteve, Viktor Dahl, Maria C Puertas, Josep M Gatell, Pere Domingo, Roger Paredes, Mark Sharkey, Sarah Palmer, Mario Stevenson, Bonaventura Clotet, Julià Blanco & Javier Martinez-Picado

With ongoing replication, integrase inhibitors may increase the levels of episomal, 2-LTR circle DNA.
Raltegravir reduced T cell activation

Very high Raltegravir level in digestive tissue
Increase in 2-LTR Circles After Raltegravir Intensification in HAART-Suppressed Patients with High CD4+ T Cell Counts: A Randomized, Placebo-Controlled Trial

H Hatano¹, M Strain², R Scherzer¹, E Sinclair¹, S Palmer³, M Busch¹,⁴, P Bacchetti¹, P Hsue¹, D Richman², S Deeks¹

¹ University of California, San Francisco, CA, USA
² University of California, San Diego, CA, and VA San Diego Healthcare System, San Diego, CA, USA
³ Karolinska Institutet, Solna, Sweden
⁴ Blood Systems Research Institute, San Francisco, CA, USA
Randomized (n=31)
VL < 40 copies/mL for ≥1 year
CD4 ≥ 350 for ≥1 year
HAART for ≥1 year

+ Raltegravir (n=15)
400mg BID
24 weeks

+ Placebo (n=16)
PBO BID
24 weeks
Increase in 2-LTR Circles in Raltegravir Group Compared to Baseline

• RGV group had a significant increase in 2-LTR circles compared to baseline
  – Ratio of week 1 to 0: 4.7 (p=0.0045)
  – Ratio of week 2 to 0: 3.4 (p=0.046)
  – Ratio of week 8 to 0: 3.6 (p=0.033)

• No substantial changes in 2-LTR circles in PBO group
Raltegravir Intensification Led to Significant Decrease in D-dimer

No change in plasma level of ultra sensitive PCR
### Therapeutics in development

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<th>CONSEQUENCES</th>
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<td>Enhance CD4 recovery</td>
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<td><em>Cure “agenda”</em></td>
<td>Maraviroc</td>
<td>Growth hormone, IL7</td>
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</table>

*Registered on clinicaltrials.gov*

Lewin S: HIV and inflammation CROI 2013
Early ART reduced inflammation
Conclusion

• Monocytes inflammation emerging as a new contributor for CV

• Raltegravir reduces HIV-inflammation:
  – Lipid friendly
  – Reduction of inflammation
  – Class effect: data pending

• Early ART remains the best way to control inflammation
Timothy Ray Brown, widely known as the Berlin patient, was effectively cured of AIDS in 2006. He had two very risky bone marrow transplants to treat leukemia and doctors believe that a special mutation in the donor's tissue conferred immunity to Mr. Brown.
AIDS IS GOING TO LOSE.