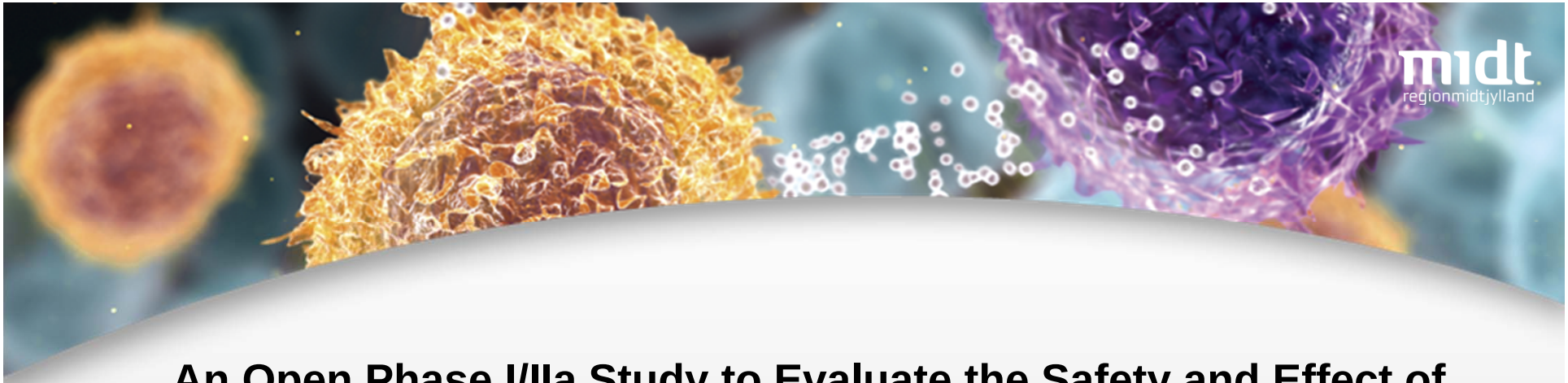

An Open Phase I/IIa Study to Evaluate the Safety and Effect of Therapeutic HIV-1 Immunization using Vacc-4x + rhuGM-CSF, and HIV-1 Reactivation using Romidepsin, on the Viral Reservoir in Virologically Suppressed HIV-1 Infected Adults on cART

"REDUC"

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Research for the future
Infectious Diseases Research Unit
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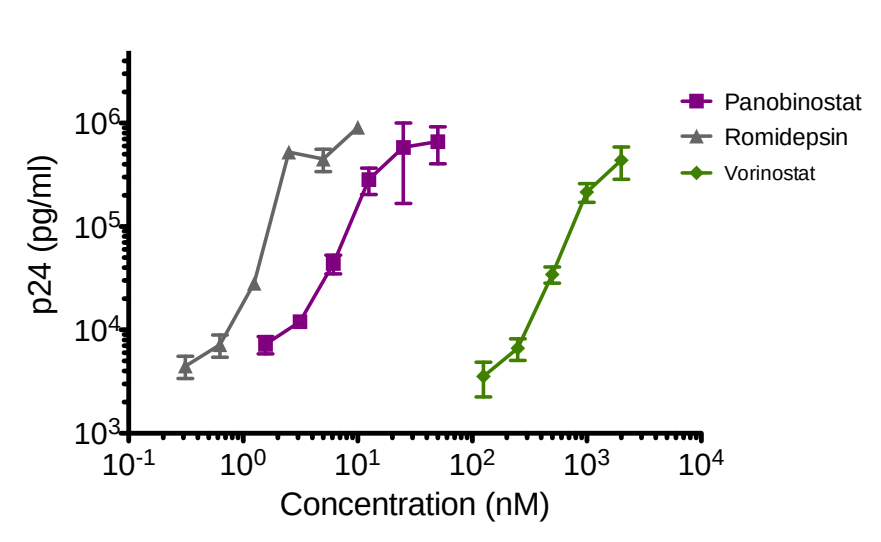
Rationale



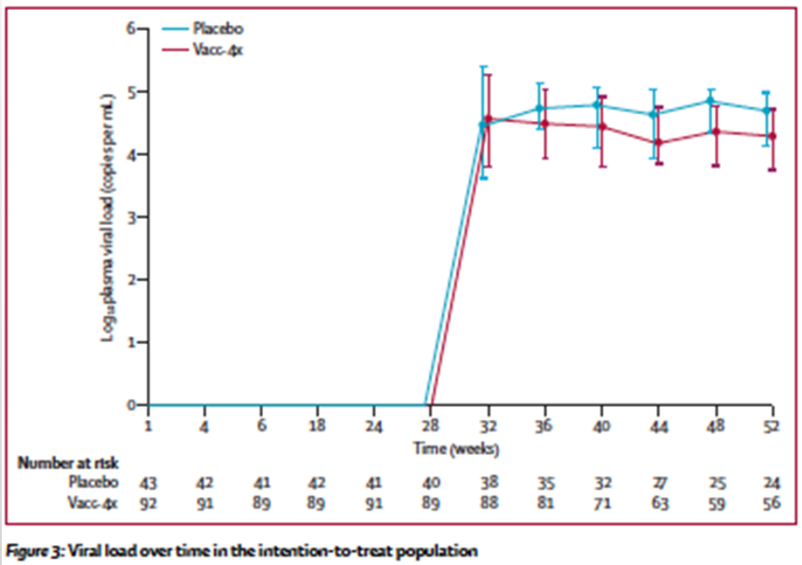
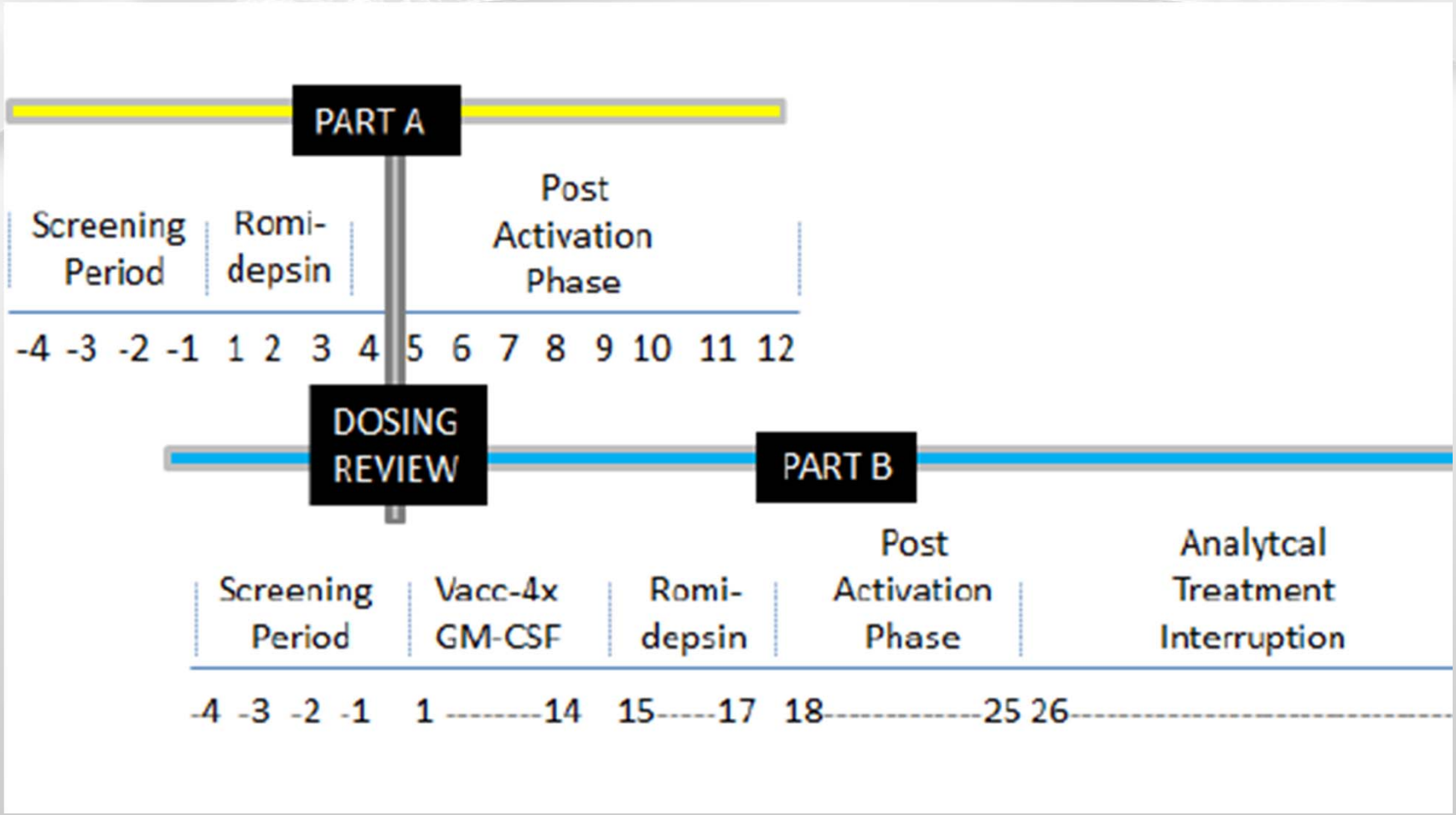


Figure 3: Viral load over time in the intention-to-treat population

Rasmussen et al. HVI 2013 (modified)
Pollard RB et al. Lancet Infect Dis 2014

REDUC study overview



Objectives and methods

Part A

Safety and tolerability of romidepsin 5 mg/m2 (one third of standard dose).

- Adverse events (AEs), Serious adverse events (SAEs), Suspected unexpected serious adverse reactions (SUSARs).
- Common Terminology Criteria for Adverse Events (CTCAE)
- Medical dictionary for regulatory activities (MedDRA)

Effect of romidepsin on HIV-1 transcription when on cART

- Cell associated unspliced HIV-1 RNA (Clear study protocol)
- Single copy assay (Method by Sarah Palmer)
- Plasma HIV RNA (NAT screen – Procleix Ultrio Plus, Genprobe)
- Plasma HIV RNA (Standard VL monitoring assay - Cobas Taqman)

Dose reviewing committee to decide proceding to part B.

Objectives and methods

Part B

- Safety
- Efficacy
  - Reduction from baseline of latent reservoir in CD4+ T cells
    - HIV-1 viral outgrowth assay (Laird et al. PLoS Path 2013)
    - Integrated HIV-1 DNA (Method by Una O´Doherty)
    - Total HIV-1 DNA by digital droplet PCR (Strain et al. PLoS One 2013)
  - Other measurements
    - T-cell activation pattern (CD69, CD25, HLA-DR, CD38)
    - Intracellular cytokine stain (IFN-gamma, IL-2, TNF-alfa)
    - IFN-gamma Elispot (Method by Giuseppe Pantaleo)
    - T-cell proliferation (Method by Giuseppe Pantaleo)
- Predictive parameters for viral control
    - HLA type, CCR5 haplotype
    - Treatment interuption (Change in viral setpoint / Time to viral rebound)

Major inclusion criteria

- Age >18 years.
- HIV-1 plasma RNA <50 copies/mL for at least 1 year with at least two viral load measures per year.
- Receiving cART, for a minimum of 1 year, defined as at least 2 nucleoside/nucleotide reverse transcriptase inhibitors plus either a non-nucleoside reverse transcriptase inhibitor, an integrase inhibitor, or a protease inhibitor.
- CD4 T-cell count ≥500 cells/mm3 at screening.
- The ability to understand and sign a written informed consent form and comply with protocol related procedures.

Major exclusion criteria

- Any significant acute medical illness in the past 8 weeks.
- History of any malignancy
- Abnormal predefined values of the hematologic and clinical chemistry at Screening
- History of insulin-dependent diabetes mellitus

- A history of clinically significant cardiac disease, symptomatic or asymptomatic arrhythmias, syncopal episodes, or additional risk factors for Torsades de pointes (e.g. heart failure, congenital long QT syndrome)
- Use of an agent definitely or possibly associated with effects on QT intervals within 2 weeks of screening
- ECG at screening that shows QTc >450 msec for males and >470 msec for women when calculated using the Fridericia formula from either lead V3 or V4

- CD4 T-cell nadir below 200 cells/ mm3 less than 2 years before study inclusion

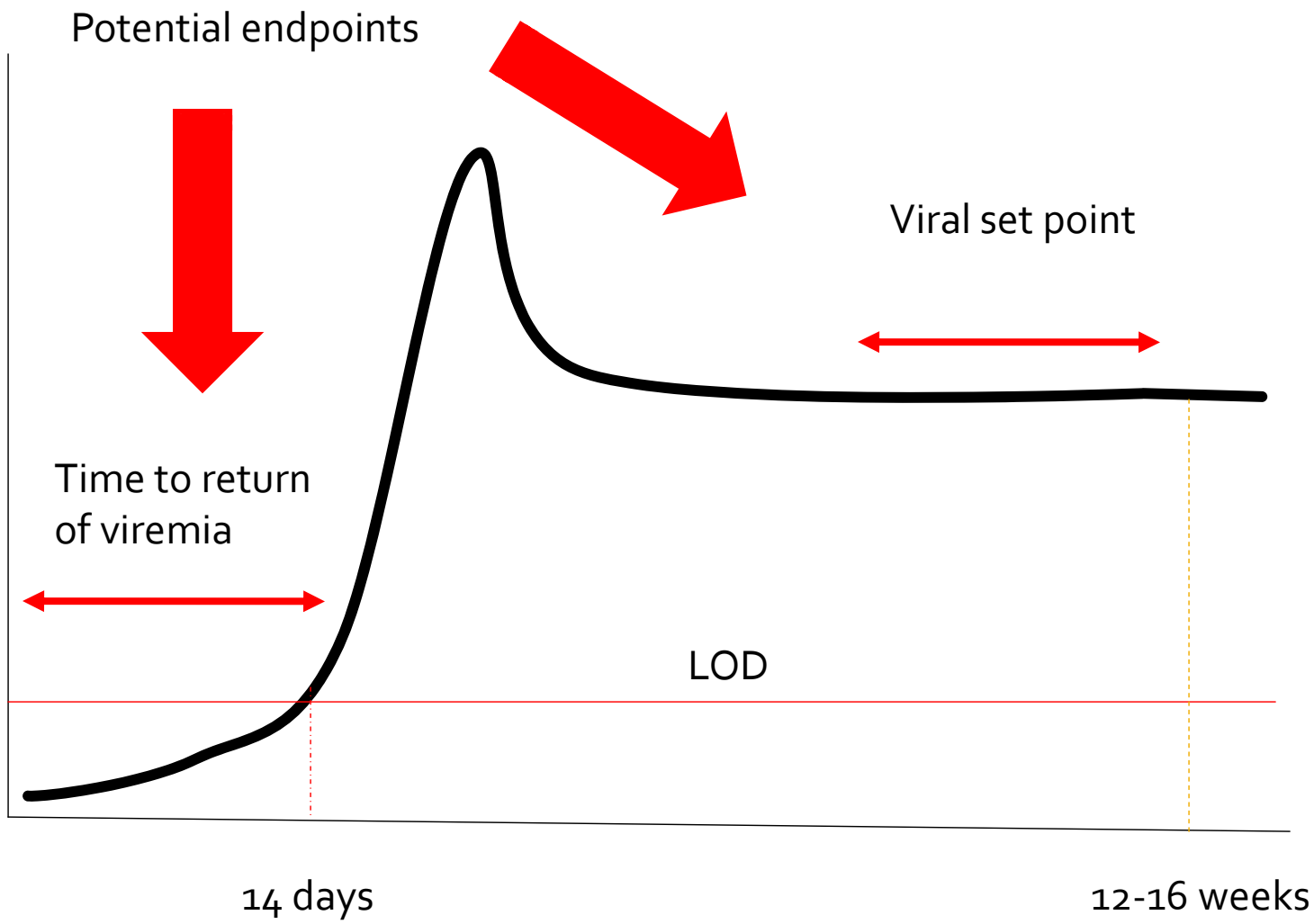
- Women of Child Bearing Potential (WOCBP) who are unwilling or unable to use an acceptable method of contraception to avoid pregnancy for the entire study period.
- Males or females who are unwilling or unable to use barrier contraception during sexual intercourse for the entire study

Rationale for ATI

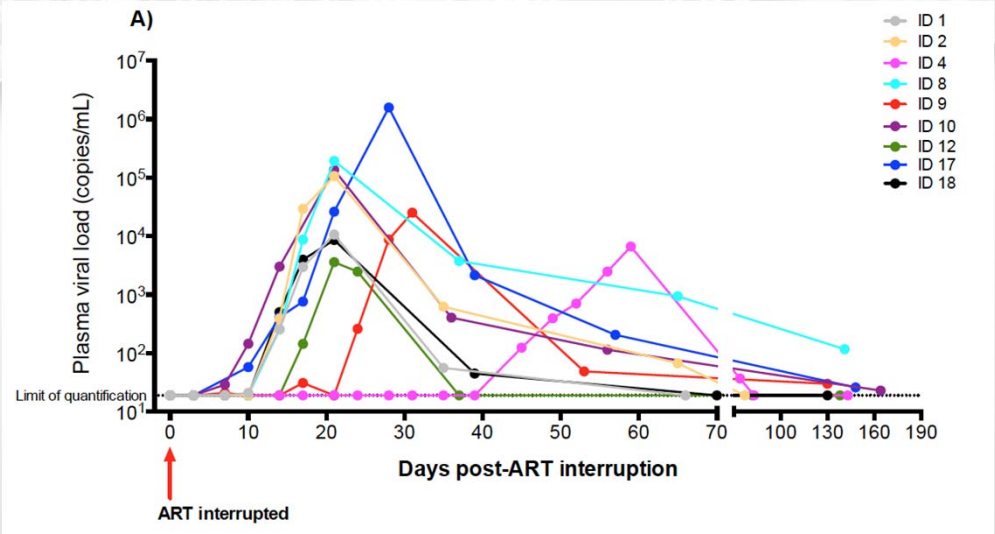
- The ultimate goal is to achieve viral control in the abscence of cART – i.e. no viral rebound in the abscence of cART.
- It will not be possible to study the predictive value of any in-vitro test/parameter if it can not be benchmarked against a clinical relevant outcome – i.e. viral control in the abscence of cART.
- Considerations of a traditional 16 weeks ATI to assess viral setpoint versus a monitored antiretroviral pause with restarting of cART at the time of viral rebound.

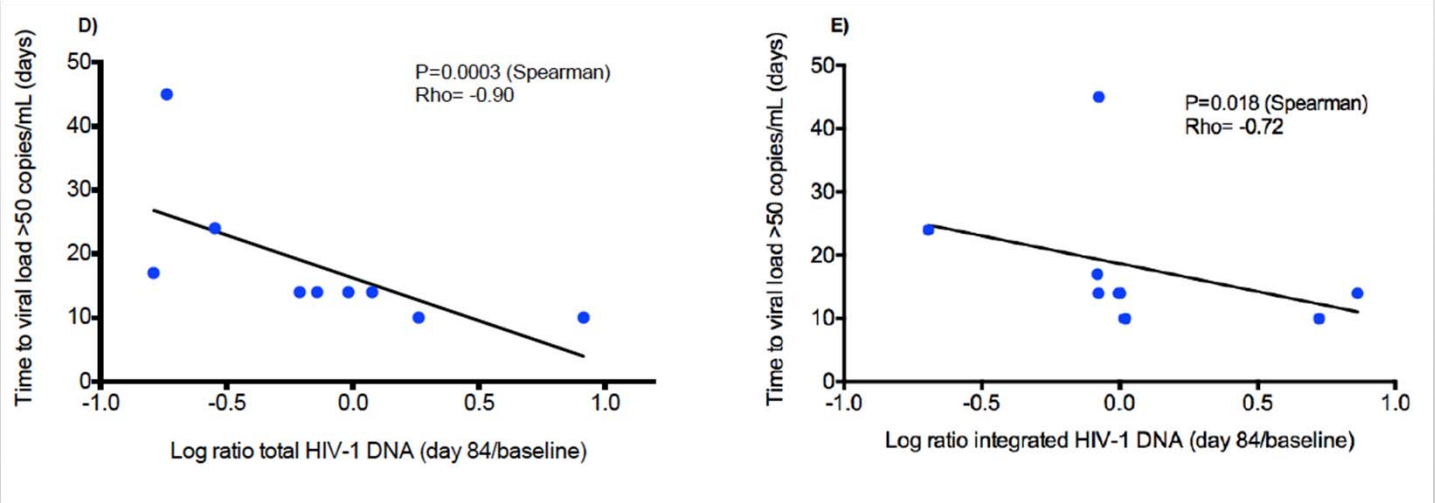
Key parameters in ATI studies

Pablo Tebas



Previous experience from the Clear-study





Rasmussen et al CROI 2014, Tolstrup et al ECCMID 2014

ATI – time to viral rebound (MAP)

Criteria for MAP

- Significant increase in unspliced HIV-RNA
- CD4+ T-cell count > 500/mm3
- Patient on NNRTI willing to swift to atazanavir

VL, CD4, clinical status, and reinforcing safe sex during MAP

- Twice weekly for the first 4 weeks
- Once weekly during the following 4 weeks
- Once every 2 weeks hereafter

Criteria for resumption of cART

- CD4+ cell-counts <350 cells/mm³
- HIV-RNA measurement >1000 copies/ml
- Subject request

Long term follow-up

All participants assessed at least every six month re.:

- Clinical status
- VL, CD4
- Clinical chemistry
- Clinical signs or symptoms of neoplasia

REDUC participants

Department of Infectious Diseases, Aarhus University Hospital, Denmark
•Ole Schmeltz Søgaard, MD, PhD
•Martin Tolstrup, MSc, PhD
•Thomas Rasmussen, MD
•Paul Denton, MSc, PhD
•Christel Rothe Brinkmann, MSc, PhD
•Rikke Olesen, MD, PhD
•Steffen Leth, MD
•Mette Graversen, MD
•Anni Winckelmann MD student
•Ann-Sofie Kjær MD student
•Lars Østergaard, Professor/Head, MD, DMSc, PhD

Bionor Pharma, Oslo,Norway
•Maja A. Sommerfelt, PhD

Ragon Institute, Harvard University/MGH, -Boston
•Mathias Lichterfeld, MD, PhD
•Maria Buzon, MSc, PhD

Westmead Millennium Institute for Medical Research, Sydney
•Sarah Palmer, PhD

University of Pennsylvania, School of Medicine
•Una O´Doherty, MD. PhD. Department of Pathology & Laboratory Medicine

Centre Hospitalier Universitaire Vaudois, University of Lausanne, Switzerland.
•Giuseppe Pantaleo, M.D

The journey of the thousand miles must begin with a single step !

Lao Tzu

Panel Discussion

- Lars Østergaard (Aarhus), presenter
- Janet Siliciano (JHMI), moderator
- Giulio Maria Corbelli (EATG)
- Romas Geleziunas (Gilead)
- Gail Henderson (UNC)
- Filip Josephson (SMPA)
- Kim Struble (CDER/FDA)

Panel Discussion Questions

- What if the intervention (not necessarily romidepsin) was genotoxic or had positive carcinogenicity findings, how would this affect patient selection, monitoring, dose selection and long term follow-up?