Combination Therapy Trials for Cure
Clinical Investigation and Trial Design

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Combined Strategies for Reduction of HIV reservoirs?

- Activation / Inflammation
  - Anti-inflammatory agents?
  - Viral Co-Infections
    - CMV?

- Improving ARV
  - Intensification
  - Tissue penetration?

- Immunity to HIV
  - Vaccines
  - Monoclonal Antibodies?

- Shock & Kill

- HIV Reservoirs
  - Latency
    - HIV reactivation: IL-7
    - Latency reactivation
      - HDACi

- Anti-immune check points?

From Katlama et al., Lancet 2013
The first steps on the three pillars of HIV persistence

- **Single strategies targeting:**
  - **Residual replication:**
    - **ARV Intensification:** Limited effect in acute ([Cheret 2015…](#)) or in chronic infection ([Buzon. 2010, the Eramune-01 & -02 studies [Katlama, 2015. Achenbach 2015]…)
  - **Boosting Immunity to HIV: Therapeutic Vaccines:**
    - rec. Poxvirus vaccine in ART-suppressed adolescents: Transient reduction in **inducible reservoir** ([Persaud 2011](#))
  - **Latent HIV reactivation:** HDACi: some activation of latently resting and memory T cells, inducing **HIV expression**
    - Vorinostat, Panobinostat: ([Archin 2012,14; Elliott 2014](#)]
    - Romidepsin: ([Schmeltz Segaard, 2014](#))

- **Is it enough?**
- **How many cycles?**
The first Combined strategies: POC Study design

- **The Eramune studies**: a common POC study design to “kick out the loser” targeting:
  - **HIV re-activation**: Eramune-01: **IL-7 + ARV Intensification** *(Katlama AIDS 2015)*
    - in 15 long-term ART suppressed chronically-infected adults:
      - => HIV re-activation but transient increase in blood ca HIV-DNA in TCM and TTM partially reflecting increased cell homeostasis *(Poglaghi, CROI 2014)*
  - **Residual replication**:
    - Eramune-02: **Therapeutic vaccine** *(VRC HIV DNA plasmid + rAd5) + ARV Intensification*
      - in long-term ART suppressed chronically-infected adults:
        - => Transient decrease in 1 patient blood total ca HIV-DNA despite robust induction of anti-HIV T cells in all *(Achenbach Lancet HIV 2015)*
  - **Others**: HIV re-activation + Residual or induced replication: in progress
    - The Bionor study: **LRA** *(Romidepsin) + Therapeutic vaccine* *(Vacc4X) : Dec 2015*
New Combined Strategies towards a remission?

Activation / Inflammation
- New Anti-inflammatory agents ??
- Kinase Inhibitors? Ex: Dasatinib?
- Immunosuppressive agents ??

Viral Co-Infections
- CMV?

Immune Activation

ARV
- Intensification?
- Tissue penetration?

Residual Replication

Immunity to HIV
- Vaccines
- Monoclonal Antibodies

Shock & Kill

HIV Reservoirs Latency

Anti-immune check points?
- Anti-PD1, PDL-1, TIGIT, Tim-3, LAG-3... ?

New LRAs ???
- Or
- Quiescent T cell activation?
- Or
- De-Repressors of transcription

From Katlama et al., Lancet 2013
Next step ? Innovating in the Shock & Kill strategy?

**In Shock strategies ?**
- Reversing Latency with Immune check-points ?
  - Success and acceptable safety in the cancer field,
- T cell re-activation using TLR7 or TLR9 agonists?
  - Acceptable safety profile

**In Kill strategies ?**
- Antibodies
  - Passive transfers of Broadly Neutralizing anti-HIV Antibodies ?
    - Single MoAbs strategies : 1\textsuperscript{st} Results expected in 2016
    - Could be combined to any “shock” : HDACi or Check point Inhib
  - Vac-3S vaccine: Preliminary data: anti-HIV gp41-3S antibodies
    - => Reduction of total ca-HIV DNA in Responders
      (R HoTsong Fang: Poster N 67)
- T cell based vaccines : still of interest :
  - Which vaccine? Rec. viral vector ? or dendritic cell based strategy?
  - Could be combined to TLR agonists
Is the Shock & Kill Strategy the unique Trick???

- Targeting HIV latency by blocking HIV transcription?
  “it seems prudent for the field to explore alternative therapeutic approaches, e.g., permanent HIV suppression that may be more feasible and efficacious.” (Dahabieh 2015)
  by targeting:
  - **Tyrosine Kinases?**
    Ex: JAK inhibitor Ruxolitinib used in cancers => End 2016
    Abl Kinase inhibitor **Dasatinib** used for CML or SAA
    inhibits HIV in vitro (Poglaghi 2013)
  - **Transcriptional repressors ?**
    Ex: **Blimp-1**: inhibits HIV transcription
    (de Masson, 2014, Kaczmarek 2014)
    Safety and Feasibility in clinical approaches ???

- **Will those strategies moving from the cancer field**
  - down modulate the reservoir size ?
  - be safe enough ?
  - require combinatorial approaches?
Next step: Which Clinical trial end-points and design?

- **Virus End-points**
  - Require solid, highly validated and reproducible assays:
    - **HIV reservoirs**
      - Total cell-associated HIV-DNA fit these criteria despite limitations (integrated vs non integrated; defective viruses...)
    - **HIV re-activation**
      - Ca-HIV transcripts assays require standardization

- **Study participants**
  - **Early treated acute infection**
    - Lower reservoirs (*Hoqueloux 2010, 13, Arantanovitch 2014....*)
    - Better anti-HIV T cell function, similar to Elite Controllers in Visconti PTCs:
      - Poster A Samri N31
  - **Chronic, long term treated infection**
    - the most frequent population

- **Study design**
  - Small POC studies “Eramune-like”?
  - ATI? Require strict follow-up and safety criteria
Are those criteria valid? The ULTRASTOP study:

- **Aim:** To investigate whether spontaneous ultra-low HIV reservoirs allows HIV remission after ATI in chronic ARV-suppressed infection?

- **Design:**
  - **Inclusion** on HIV-DNA levels <100 cp/million PBMCs + normal immune status
  - **ATI** in successive 5 patients cohorts if ≥ 1 remission after 6 months.

- **Results:** 
  - **1 remission / 10 patients:** with HIV-RNA <400 cp/mL for >48 weeks
  - In an HLA-B*27+ PTC (but B*27 or*57 in 5/10) without anti-HIV T cells detectable at baseline but boosted after ATI

- **Conclusion:**
  - **10% Remission rate** close to the 12% estimate in VISCONTI; HLA-B*27 genetic bias ???
  - **Safe design:** no significant HIV-DNA changes from baseline; No severe adverse events

Should we pursue Cure strategies aiming only at decreasing HIV reservoirs?