Combination Therapy Trials for Cure

Clinical Investigation and Trial Design

towards an HIV cure
people focused
science driven

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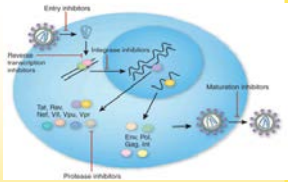
Combined Strategies for Reduction of HIV reservoirs ?

Activation / Inflammation
✓ Anti-inflammatory agents ?

Viral Co-Infections
✓ CMV?

Improving ARV



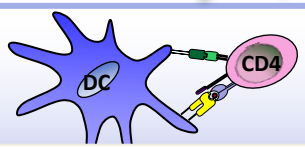
✓ Intensification
✓ Tissue penetration ?

Immunity to HIV
✓ Vaccines
✓ Monoclonal Antibodies ?

Immune Activation

Residual Replication

Shock & Kill



Anti-immune check points ?

HIV Reservoirs Latency

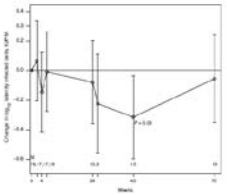
HIV reactivation: IL-7

Latency reactivation HDACi

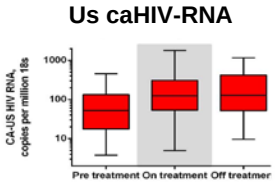
From Katlama et al., Lancet 2013

The first steps on the three pillars of HIV persistence

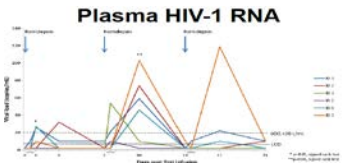
- **Single strategies** targeting:
  - **Residual replication** :
    - **ARV Intensification** : Limited effect in acute *(Cheret 2015…)* or in chronic infection *(Buzon. 2010, the Eramune-01 & -02 studies [Katlama, 2015. Achenbach 2015]…)*
    - **Boosting Immunity to HIV: Therapeutic Vaccines**:
      - 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**; Eliott 2014:***



SAHA



Romidepsin

    - 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 ?

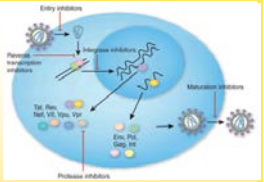
Activation / Inflammation

New Anti-inflammatory agents ??

Kinase Inhibitors ? Ex: *Dasatinib?*

Immunosuppressive agents ??

ARV



- ✓ Intensification ?
- ✓ Tissue penetration ?

Immunity to HIV

- ✓ **Vaccines**
- ✓ **Monoclonal Antibodies**

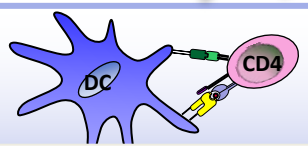
Viral Co-Infections

✓ **CMV?**

Immune Activation

Residual Replication

Shock & Kill



Anti-immune check points ?

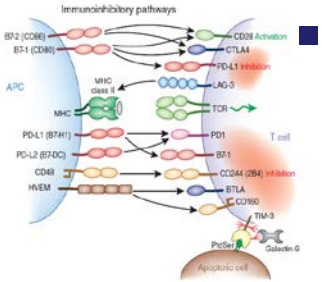
Anti-PD1, PDL-1, TIGIT, Tim-3, LAG-3… ?

HIV Reservoirs Latency

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

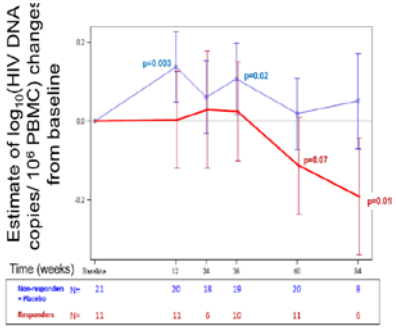
- **In Kill** strategies ?
  - **Antibodies**
    - ✓ **Passive transfers of Broadly Neutralizing anti-HIV Antibodies** ?

      Single MoAbs strategies : 1st 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

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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

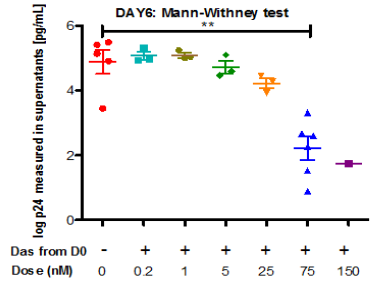
    Abl Kinase inhibitor **Dasatinib** used for CML or SAA inhibits HIV in vitro *(Poglaghi 2013)*

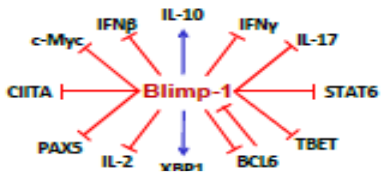
  - **Transcriptional repressors ?**

    Ex: **Blimp-1**: inhibits HIV transcription

    (de Masson, 2014, Kaczmarek 2014)

    Safety and Feasibility in clinical approaches ???



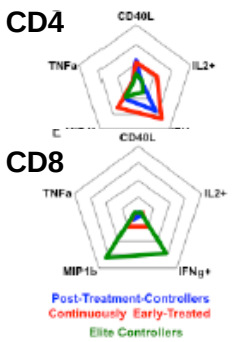


- ***Will those strategies moving from the cancer field***
  - ***down modulate the reservoir size ?***
  - ***be safe enough ?***
  - ***require combinatorial approaches?***

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

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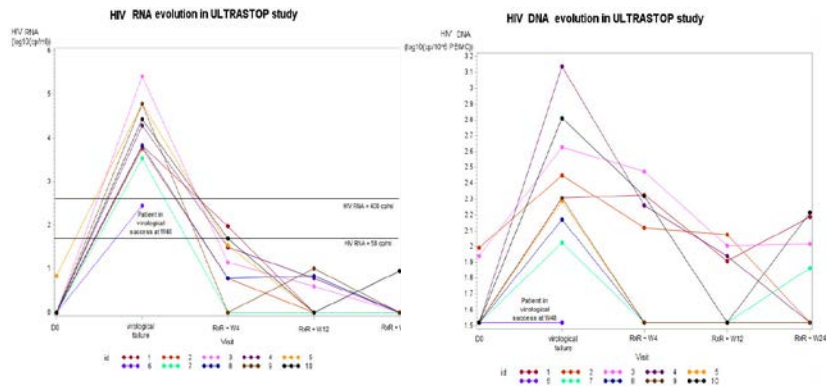
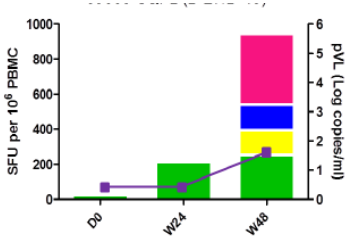
Are those criteria valid? The ULTRASTOP study:

- 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**



n an **HLA-B*27+ PTC** (but B*27or*57 in 5/10)

without anti-HIV T cells detectable at baseline but boosted after ATI



Posters R Calin N64 , C Hamimi N37

- 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?