Translational HIV/AIDS research: past successes and futur challenges

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27 years of HIV translational science...

1983

- Identification/Characterization of HIV-1 and viral antigens
- HIV target cells and HIV pathogenesis
- Characterization HIV-1 replication cycle

Diagnostic Tests
- First step for prevention and treatment
- Immune cell makers as prognosis and monitoring tests
- Drug discovery for prevention and therapy
- Monitoring tests for Viral load and ARV resistance

2010

Characterisation HIV-1 genome and of its diversity
The Power of HAART: Demographic Model

HIV prevalence

Cost of treatment

Number of infections prevented

Montaner et al, Lancet 2006
Challenges in HIV/AIDS Research in 2010…

**NORTH**

**CHRONIC HIV INFECTION**

**NON AIDS MORTALITY**

Mortality rate almost identical to the general population…

- Viral latency, HIV reservoirs
- Inflammation, activation, insufficient immune restoration on HAART
- Complications associated to long term HAART including:
  - Cardiovascular diseases (8%), cancers (15,4%), liver diseases (7%)…
  - Neurological disorders, Aging diseases (osteoporosis, Alzheimer…)

**SOUTH**

**AIDS MORTALITY**

8 to 26% of patient mortality during the first year of treatment initiation...

- Access to HAART *(including 2nd and 3rd line treatment)*
- PMTCT *(only 45% of pregnant women on HAART)*
- Monitoring patients on HAART *(access to viral loads, drug resistance tests…)*
- Coinfections and IRIS: Tuberculosis (21%), meningitis Cryptococosis (20%), Viral hepatitis, CMV…

**Early Testing, Prevention (Microbicides? PreP? Vaccine?), Treatment (TasP?)**

Needs for further international efforts and for further research for preventive and therapeutic strategies
Rapid rebound in virus when HAART stopped

Years on HAART

off HAART

HIV RNA

CD4 count

50

0 1
HIV reservoirs on HAART...

Very early establishment after the infection

**Which cells?** Predominantly $T_{CM}$ et $T_{TM}$ also monocyte/macrophages, astrocytes....

**Where?** Blood, Gut or brain (inaccessibility to drugs + high number of activated immune cells)

Why?

- Viral replication
- T cell survival
- Proliferation

*Courtesy of Nicolas Chomont*

How?
Potential strategies targeting HIV reservoirs

Unlocking latency mechanisms (*Histone deacetylase inhibitors*, *Vorinostat*, *methylation inhibitors*like *5-aza-dC*...)

Use of immuno-modulating agent (*cytokines* like *IL2, IL7, Maraviroc, PD1-antibody to target CD4 T<sub>CM</sub>*...) in *HAART pts*

Enhancement of anti-HIV immunity (*therapeutic immunization using DNA w/wo lipopeptides, rMVA, targeted DC*...)

Antiretroviral drugs with improved penetration and potency (*shRNA tat, rev, TAR*...)

Intensifying antiretroviral treatment (*raltegravir, dorunavir/r, Truvada*...)

Early intense HAART with *raltegravir, dorunavir/r, maraviroc associated with Truvada in primoinfected pts*..(*Optiprim*)

Achieving functional cure?

Permanent suppression of viral replication without eradicating the virus from the body
Why it should be possible to obtain a functional cure for HIV/AIDS?

• A decrease in viral load is clearly associated with clinical benefit

• A small percentage (<0.3%) of HIV-1-infected subjects show no disease progression and/or spontaneous control of viral replication (e.g. long-term nonprogressors and “HIV Controllers”)

• African monkeys infected by SIV are naturally protected against disease progression
The IAS decided to stimulate, coordinate and support a multidisciplinary working group to elaborate an International Scientific Strategy.

A Global Scientific Consortium « Towards an HIV Cure » supported by International organizations in 2012?
<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
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<tbody>
<tr>
<td>August 1987</td>
<td>1st phase I trial</td>
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<tr>
<td>1987-2007</td>
<td>&gt; 110 trials (10 Phase II/III) with 67 products (27 500 volunteers)</td>
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<tr>
<td>2003</td>
<td>Data of the 1st phase III efficacy trial VaxGen</td>
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<tr>
<td>Sept. 2007</td>
<td>STEP/Phambili phase IIb trial (HIV-1B gag, pol, nef / rAd5)</td>
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<tr>
<td>Oct. 2009</td>
<td>RV144 “Thai”: ALVAC (gag/pol/env) + AidsVax (B/Ergp120)</td>
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</table>

Candidate vaccine are usually safe and showed some degree of immunogenicity.

Lack of efficacy of rgp120 definitively proven.

Discontinued for lack of efficacy.

Very Modest Efficacy (31%).

Ongoing phase II trials (DNA+MVA, DNA+NYVAC, lipopeptides...).
• Vaccines are effective against other viral diseases

• There is evidence that very few individuals are protected against HIV-1 infection (*e.g.* exposed non-infected subjects)

• Some experimental vaccines confer protection to monkeys infected with SIV

• Recent identification of new neutralizing epitopes using trimeric and/or HIV-1 env

• Certain vaccine candidates may induce immune responses in vaccinees without any major adverse event

• One vaccine prime-boost strategy showed for the first time a modest efficacy (31% of protection in the Thai-RV144 vaccine efficacy trial)
Global HIV Vaccine Enterprise

Promoting innovation and collaboration to speed the search for an HIV vaccine
# 10 Challenges of HIV Vaccine R&D

1. Unify basic, preclinical and clinical research
2. Develop data infrastructure for rapid sharing
3. Bring in new minds and new ideas
4. Broaden and increase funding
5. Enhance trial design
6. Develop world capacity
7. Engage communities
8. Assess impact of prevention trial results
9. Realize potential of non human primate models
10. Engage industry
Effectiveness of available tools for prevention:

- Condom use: 60-96% (de Vincenzi 1994 ... Wang 2010)
- Microbicidies using ART (39 -54%, CAPRISA 2010)
- PreP in MSM: 44% reduction of HIV incidence (iPrEx study; NEJM 2010)
- Needles exchange + fight against discrimination decrease in incidence of HIV among IVDUs in Europe (Lancet 2010)
- Decrease in prevalence in populations where ART is highly used (Fang 2004, Montaner 2010, Das 2010, Bezemer 2010)
- Mathematical models on TASP efficacy (Granich 2009, Case 2010)
Combined prevention strategies to reduce the HIV-1 epidemic...

- Behavioral change
- Biomedical strategies
- Social justice and human rights
- Treatment/Antiretroviral/STI/Antiviral

UNAIDS Declaration « Prevention Revolution », December 1st, 2010

Leadership and scaling up of treatment/prevention efforts

Community involvement

Call for Universal Policy for Harm reduction, Testing, Counseling, Treating and Assessing for efficacy by monitoring the incidence of HIV infection
New Challenges: HIV and emerging new diseases...

Cancer, lymphomas
Ageing diseases
Cardiovascular diseases

Immune defects, inflammatory and autoimmune malignancies
HIV Infection
Chronic on HAART
Non AIDS related mortality

Learning from each others beyond HIV/AIDS…..
Fighting against HIV/AIDS based on scientific evidences
A driving force in global health equity

<table>
<thead>
<tr>
<th>RISKS PREVENTION</th>
<th>Condom (other STI), clean needles (HCV), Drug injecting facilities (\textit{reduced overdoses, abscesses, skin infections, thrombosis})</th>
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</thead>
<tbody>
<tr>
<td>PMTCT</td>
<td>Contributes directly to 4 of the MDGs where HIV is currently holding back progress (\textit{gender equity &amp; empower women, reduce child mortality, improve maternal health, Combat HIV/AIDS})</td>
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<td>UNIVERSAL ACCESS TO TREATMENT</td>
<td>Improvements and decentralization of health services, Organization of supply chain, Task shifting, Promote innovative solution for financing health development in resource limited countries (\textit{UNITAID patent pool, tax on financial transaction…})</td>
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<td>HUMAN RIGHTS</td>
<td>Fighting for an equitable access to care of the most vulnerable and marginalized population (\textit{prostitutes, drug-users, MSM, prisoners…})</td>
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New discoveries in HIV/AIDS can impact Global Health!

New challenges, new concepts, new technologies…
A new generation of players…
But keeping in mind…
All together like in the early years!!!