Successes and challenges in HIV science.

Pr. Jean-François DELFRAISSY
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Internal Medicine Department
CHU Bicêtre – Paris XI - ANRS
More than 30 years of HIV Science
A good example of translational research

A new era since cART in 1996....

F.Barre Sinoussi, AL Ross, JF Delfraissy Nature Microbiology 11.2013
A unique engagement of patients representatives for the universal access to treatment

Evolution of 1st line treatment price (MSF)

Generic competition and activists pressure = drastic reduction of ARV prices in ressource-limited countries but still too few combination available + 2nd/3rd line treatments prices too high!

Today: The revolution of Hepatitis C treatment!
New fight to achieve universal access at an affordable price to save lifes...

1.6 million in a year

Goal set by UN in 2011

9.7 millions

+ 1.6 million in a year

34.2 millions of PLWHIV (23.5 in sub Saharan Africa)

2013 OMS treatment guidelines: 26 millions HIV+ people now eligible for treatment initiation

4.2 millions death avoided thanks to ARVs!
Key Challenges and Priorities in HIV/AIDS today

IMPLEMENTATION:

- Prevent new infections in uninfected people (*education, condoms, circumcision, risk reduction...*)
- Test, treat and retain 30-50% of HIV+ people ignore their status..... Cascade of continuum of care

- Strengthen health systems (*link prevention, care and treatment services*)
- International Investments
- Political willingness
- Leadership/governance
- National integrated policies
- Bridging programs (*communities, implementers, health workers, researchers...*)
- Fighting stigma/discrimination/......
What can we do to improve the situation?

<table>
<thead>
<tr>
<th>step</th>
<th>targeting</th>
<th>intervention examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing</td>
<td>HIV testing capacity; demand for HIV testing; completion of staging and linkage to ART care</td>
<td>decentralisation of testing; self-testing; targeted testing in high risk groups</td>
</tr>
<tr>
<td>pre-ART care</td>
<td>retention in pre-ART care prior to ART eligibility</td>
<td>task shifting; transport allowance; earlier initiation</td>
</tr>
<tr>
<td>ART care</td>
<td>increase retention; increase reinitiation for treatment interrupters</td>
<td>support tools; home-delivered ART; health information systems for tracking LTFU</td>
</tr>
</tbody>
</table>

ongoing implementation research is essential

Kranzer et al; JIAS 2012
## Prévalence du VIH en 2010

<table>
<thead>
<tr>
<th></th>
<th>Nb de PVVIH</th>
<th>Taille population 18-64 ans</th>
<th>Taux de prévalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HSH</strong></td>
<td>53 100</td>
<td>312 300</td>
<td>17,00 (16,39-17,80)</td>
</tr>
<tr>
<td></td>
<td>(51200-55600)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>UDI</strong></td>
<td>14 200</td>
<td>81 000</td>
<td>17,53 (15,93-20,62)</td>
</tr>
<tr>
<td></td>
<td>(12900-16700)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Femmes hétérosexuelles étrangères</strong></td>
<td>20 300</td>
<td>1 296 400</td>
<td>1,57 (1,43-1,74)</td>
</tr>
<tr>
<td></td>
<td>(18600-22600)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hommes hétérosexuels étrangers</strong></td>
<td>13 700</td>
<td>1 312 900</td>
<td>1,04 (0,87-1,25)</td>
</tr>
<tr>
<td></td>
<td>(11400-16400)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Femmes hétérosexuelles françaises</strong></td>
<td>22 300</td>
<td>18 752 800</td>
<td>0,12 (0,11-0,13)</td>
</tr>
<tr>
<td></td>
<td>(19700-24600)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hommes hétérosexuels français</strong></td>
<td>22 000</td>
<td>17 811 400</td>
<td>0,12 (0,10-0,15)</td>
</tr>
<tr>
<td></td>
<td>(18400-26500)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Autres</strong></td>
<td>3 800</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(3000-4700)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Hommes</strong></td>
<td>100 600</td>
<td>19 517 600</td>
<td>0,51</td>
</tr>
<tr>
<td><strong>Total Femmes</strong></td>
<td>48 800</td>
<td>20 049 200</td>
<td>0,24</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>149 500</td>
<td>39 566 800</td>
<td>0,37 (0,36-0,39)</td>
</tr>
<tr>
<td></td>
<td>(143000-155800)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Nombres et caractéristiques des VIH+ qui ignorent leur séropositivité en 2010

<table>
<thead>
<tr>
<th></th>
<th>Nb personnes vivant avec le VIH non diagnostiquées (IC à 95%)</th>
<th>Taux prévalence VIH non diagnostiquée pour 10000 (IC à 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td><strong>29000</strong>&lt;br&gt;(24200-33900)</td>
<td><strong>7</strong>&lt;br&gt;(6-9)</td>
</tr>
<tr>
<td><strong>HSH</strong></td>
<td>9200&lt;br&gt;(7800-11200)</td>
<td>295&lt;br&gt;(250-359)</td>
</tr>
<tr>
<td>Hétérosexuels français</td>
<td>10000&lt;br&gt;(6400-13900)</td>
<td>3&lt;br&gt;(2-4)</td>
</tr>
<tr>
<td>Hétérosexuels étrangers</td>
<td>9300&lt;br&gt;(7000-11900)</td>
<td>36&lt;br&gt;(27-46)</td>
</tr>
<tr>
<td><strong>UDI</strong></td>
<td>500&lt;br&gt;(100-1100)</td>
<td>62&lt;br&gt;(12-136)</td>
</tr>
<tr>
<td><strong>Total Hommes</strong></td>
<td><strong>20300</strong>&lt;br&gt;(16600-24500)</td>
<td><strong>10</strong>&lt;br&gt;(9-13)</td>
</tr>
<tr>
<td><strong>Total Femmes</strong></td>
<td>8700&lt;br&gt;(6100-11000)</td>
<td><strong>4</strong>&lt;br&gt;(3-5)</td>
</tr>
</tbody>
</table>
Futurs défis

- Réduire le temps entre l’infection et le diagnostic → réduire le diagnostif tardif

Source : InVS
Cascade de la prise en charge en France en 2010

Today a huge challenge is to test, treat and retain under treatment

30 to 50% of HIV+ people ignore their serological status

Majority of PLWHIV is not treated

- Testing coverage is low and inadequate linking between testing & care
- Late diagnostic & treatment initiation, low retention into care

Piot and Quinn, NEJM 2013
Micek et al., JAIDS 2009
Gardner et al., CID 2011
Hall et al., JAMA IM 2013
AGENDA of the ANRS:
4 main priorities for HIV

- Testing: Novel methods; Early and better treatment
- Prevention of new infection with a biomedical approach
- Develop new vaccine strategies
- Study reservoirs with the objective of eradication or functional cure

With a NORTH ↔ SOUTH vision
Integrating economic aspects
Tenofovir is a First-Generation PrEP Agent: We Must Move Forward Smartly

PrEP Efficacy Estimates from 0-75%...
What is the best strategic use of tenofovir-based PrEP?

Landmark health research is a process of continued development

We need a choice of strategies to meet different needs

Adherence remains important with less user-dependent strategies (i.e., vaginal rings & injectable PrEP...)
Conflicting Results with Daily Oral PrEP

Efficacy (95% CI)

- TDF for HIV discordant couples (Partners PrEP)
  - FTC/TDF for HIV discordant couples (Partners PrEP)
  - TDF for young heterosexuals (TDF-2)
  - TDF/FTC for injecting drug users (Bangkok TDF)
  - TDF/FTC for MSM and TW (iPrEx)
  - TDF/FTC for women (FEM-PrEP)
  - TDF/FTC for women (VOICE)

Ipergay Enrollment (Sep 3, 2014)

Number of participants

Nb pré-inclus = 410
Nb randomisés = 372

Regions:
- CANADA: 42
- TENON: 60
- ST-LOUIS: 154
- NANTES: 13
- NICE: 29
- TOURCOING: 27
- LYON: 78

Agence autonome de l’Inserm
New Challenges: HIV and emerging new diseases...

- Cancer, lymphomas
- Aging 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.....
HIV infection

Early Antiretroviral treatment

Inflammation & Chronic activation

Therapeutic options targeting host factors/responses?

+ Efficient immune function? Low HIV reservoirs?

Prevent AIDS
Improve quality of life
Prolong life

Functional Cure?

Steven Deeks, IAS 2013
Cabotegravir (GSK 12,65,744)

Introduction

- Cabotegravir (CAB, GSK1265744) is an investigational integrase DNA strand transfer inhibitor (INI)
  - Raltegravir, elvitegravir and dolutegravir are approved oral INIs
- Long-acting (LA) Formulation
  - 200 mg/mL nanosuspension
- Indications under study
  - HIV Treatment:
    - Maintenance strategy in suppressed patients (2-drug LA regimen)
    - CAB LA partner agent is rilpivirine (RPV); TMC278 LA (Janssen)
    - Once every 4 or 8 weeks IM injection
    - Potential for improved adherence, impacting efficacy
  - HIV Pre-exposure Prophylaxis (PrEP):
    - Potential for use as single agent given once every 12 weeks
    - Improved adherence associated with higher rates of protection in PrEP studies of other agents

LATTE: GSK1265744 as Part of ART in Naive Pts: Results of 24-Wk Induction

- GSK1265744 (744), DTG analogue with long half-life, oral or injectable formulations
- Randomized, dose-ranging phase IIb study of oral formulation
- Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48

**Induction Phase**

<table>
<thead>
<tr>
<th>ART-naive pts, HIV-1 RNA &gt; 1000 c/mL (N = 243)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratified by HIV-1 RNA (≤ vs &gt; 100,000 c/mL) and NRTI</td>
</tr>
</tbody>
</table>

**Wk 24**

- 744 10 mg QD + 2 NRTIs† (n = 60)
- 744 30 mg QD + 2 NRTIs† (n = 60)
- 744 60 mg QD + 2 NRTIs† (n = 61)
- EFV 600 mg QD + 2 NRTIs QD (n = 62)

**Wk 48**

- 744 10 mg QD + RPV 25 mg QD
- 744 30 mg QD + RPV 25 mg QD
- 744 60 mg QD + RPV 25 mg QD

*Pts with HIV-1 RNA < 50 c/mL at Wk 24 continued to maintenance phase.
†TDF/FTC or ABC/3TC.

LATTE: Virologic Success During Induction and Maintenance Phases

2 pts with PDVF during maintenance; both with INSTI mutations at BL

<table>
<thead>
<tr>
<th>HIV Vaccine discovery</th>
<th>Comorbidities on ART</th>
<th>HIV Cure discovery</th>
</tr>
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<tbody>
<tr>
<td>Still no correlates of protection but significant progresses in HIV vaccine research open new perspectives: Thai trial, very potent broadly neutralizing Ab, protection in macaques…</td>
<td>HIV is now a chronic condition on life long HAART but non AIDS related comorbidities linked to persistent inflammation/chronic immune activation… new therapeutic strategies</td>
<td>Persistent HIV infection on HAART is the main hurdle science must tackle to achieve an HIV “Cure”</td>
</tr>
</tbody>
</table>

**MANY other CHALLENGES...**

- Novel creative ideas
- Multi-disciplinary collaborations
- Partnerships between private & public sectors
- International coordination
- Fundings
- /.....
• Identification of new very potent broadly neutralizing antibodies in HIV+ patients (“elite neutralizers”), structurally and functionally characterized.

• Identification of new sites of vulnerability of HIV env (MPER, CD4bs, V1/V2 and V3, glycan side chain on outer domain)

• Non neutralizing but protective antibodies (ADCC, Fc-mediated, others…)?

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• Structure-based immunogen design & novel delivery systems

• Gene transfer and genetic engineering of T cells
Experimental vaccines induce protection in SIV infected macaques

Protection obtained by passive immunization in diverse models

Therapeutic efficacy of potent neutralizing HIV-1-specific monoclonal antibodies in SHIV-infected rhesus monkeys

Passive transfer of modest titers of potent and broadly neutralizing anti-HIV monoclonal antibodies block SHIV infection in macaques

Combine vaccine candidates to elicit conventional and non-conventional protective responses.

Combine vaccine therapy to other strategies in HIV cure research.
<table>
<thead>
<tr>
<th>Eradication</th>
<th>Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterilizing Cure</td>
<td>Functional Cure</td>
</tr>
<tr>
<td>Elimination of all latently infected cells</td>
<td>Long-term health without cART &amp; without risk of transmission</td>
</tr>
</tbody>
</table>

- Berlin patient
- Proof of concept
Why do we are optimistic about at least a Functional Cure (life-long remission)?

**Natural protection against AIDS** of African NHP infected by SIV related to an attenuated immune activation: *no microbial translocation and no gut destruction; restricted infection of memory CD4 T cells; distinct innate immune response to SIV, in particular at the level of pDC and type I IFN*

**Bone Marrow Transplantations:** Proof of concept from the Berlin patient (*BMT with CCR5Δ32 stem cells*), 2 Boston Patients. Some data show *no efficacy on viremia & DNA level after BMT in 10 patients* (*Cillo AR et al, JAIDS 2013*) and *relapse of HIV viremia after ART cessation in the Boston patients*.

**HIV Controllers:** <0.3% of HIV+ people, treatment naïve naturally control infection (undetectable VL; low level of reservoirs): *very efficient suppressive CD8 response; restricted infection of their CD4 cells and macrophages; genetic factors*.

**Cases of “Functional” cure after very early treatment:** “Mississippi baby” treated 30h after birth for 18 months, 27 months of control off treatment before relapse of viremia; ANRS EP 47 VISCONTI (*Saez-Cirion et al, PloS Pathogens 2013*): 20 HIV+ patients treated about 10 weeks PI for 3 years, ≈9 years of control off treatment.
Why it’s time to accelerate HIV cure research now?
A better knowledge on HIV pathogenesis...

Rapid seeding of the viral reservoir prior to SIV viraemia in rhesus monkeys

James B. Whitney¹,², Alison L. Hill³, Srisowmya Sanisetty¹, Pablo Penaloza-MacMaster¹, Jinyan Liu¹, Mayuri Shetty¹,
Lily Parenteau¹, Crystal Cabral¹, Jennifer Shields¹, Stephen Blackmore¹, Jeffrey Y. Smith¹, Amanda L. Brinkman¹, Lauren E. Peter¹,
Sheeba I. Mathew¹, Kaitlin M. Smith¹, Erica N. Borducchi¹, Daniel I. S. Rosenbloom³, Mark G. Lewis⁴, Jillian Hattersley⁴, Bei Li⁵,
Joseph Hesselgesser⁵, Romas Geleziunas⁵, Merlin L. Robb⁶, Jerome H. Kim⁶, Nelson L. Michael⁶ & Dan H. Barouch¹,²

- Viral load
- HIV-specific CD8 T cells
- CD4 count (blood)
- CD4 count (blood)
- Generalized immune activation
- Set points
- Viral reservoirs & replication
- Inflammation & immune activation

2-3 weeks 3-10 weeks > 6 months
Acute infection Chronic infection
Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission after the Interruption of Early Initiated Antiretroviral Therapy ANRS VISCONTI Study

Asier Sáez-Cirión¹*, Charline Bacchus², Laurent Hocqueloux³, Véronique Avettand-Fenoel⁴,⁵, Isabelle Girault⁶, Camille Lecuroux⁶, Valerie Potard⁷,⁸, Pierre Versmisse¹, Adeline Melard⁴, Thierry Prazuck⁷, Benjamin Descours², Julien Guergnon², Jean-Paul Viard⁵,⁹, Faroudy Boufassa¹⁰, Olivier Lambotte⁶,¹¹, Cécile Goujard¹⁰,¹¹, Laurence Meyer¹⁰,¹², Dominique Costagliola⁷,⁸,¹³, Alain Venet⁶, Gianfranco Pancino¹, Brigitte Autran², Christine Rouzioux⁴,⁵*, the ANRS VISCONTI Study Group

Perspectives
- Mechanisms of the viral control?
- What are the predictors of this very specific status?
- Can we increase the numbers?
- International Cohort I-Visconti
Post-treatment controllers have an extremely weak HIV-1 reservoir

Lewin and Rouzioux AIDS, 2011
Rouzioux & Richman, 2012
Delta ADN-VIH (log$_{10}$) copies/million PBMC de J0 à M24 en ITT : OPTIPRIM ANRS147

Cinétique de décroissance de l’ADN-VIH strictement identique dans les deux bras

- OPTIPRIM M12: Arm1 -1.26  Arm2 -1.24 et 25% des patients < 2 log10 copies/million PBMC .
- ANRS PRIMO Cohort: N=325 patients M12: -0.81 [-1.14;-0.51] (data from the Primo cohort)
- Quest trial, N=56 patients M12: -1.1 [-1.6;-0.8] (B.Hoen, CID 2007)
- Patient chroniques: 0.7 à 5ans (JP. Viard et al, AIDS 2004) A.Chéret & al, Article 3
Can we cure HIV with latency “reactivation” drugs?

- NF-kB activators (*Prostratin, PMA, TNFα*)
- HDAC inhibitors (*VPA, Vorinostat in phase 3*)
- Jak/Stat pathway (*IL7*)
- Akt/HEXIM-1 modulators (*Hexamethylbisacetamide HMBA*)
- Methylation inhibitors (*5-aza-2’-deoxycytidine or 5-aza-dC*)

Vorinostat in cART treated patients *(D. Margolis et al, Nature 2012, Lewin S, CROI 2013)*: Latency can be reversed by HDAC inhibitor?
Other more potent HDACi studied in clinical trials *(Romidepsin, Panobinostat in Danemark)*

BUT Probably not enough.....
Keeping in mind!

We have been and we will be stronger altogether!!
Great successes, but endless challenges....

1980: Official eradication of smallpox related to universal access to vaccination.


New concept of Global Health...
Ebola, a call for action

Ebola: time to act

Governments and research organizations must mobilize to end the West African outbreak.

11 September 2014 | Vol 513 | Nature | 143

Ebola: learn from the past

Drawing on his experiences in previous outbreaks, David L. Heymann calls for rapid diagnosis, patient isolation, community engagement and clinical trials.

16 October 2014 | Vol 514 | Nature | 299
ACKNOWLEDGMENTS

- Clinical and research teams, ESTHER
- Chairs of Coordinated working groups
- ANRS staff
- Patients NGOs, more specifically TRT5, AIDES, Sidaction
- INSERM, Institut Pasteur, IRD, CNRS, Hospitals
- Pharmaceutical Industry
- Foundations
- Patients
2 years later in May 1983: First report on HIV...
1. 1983-1984: Convince scientific community and authorities that LAV was the etiological agent of AIDS

- Link between the virus and the AIDS disease (viral isolate, sero-epidemiological investigation)
- Characterization of LAV and other viral isolates.

2. 1983-1985: Develop serological tests for diagnosis

- Stop any other research programs in our lab
- Mobilize others (Clinicians, nurses, virologists, immunologists, biochemists, molecular biologists...)
- Patients...

Mobilize the private sector....
WHO: persons receiving ART 2003-2015

Actual and projected numbers of people receiving ART in LMIC

2013 Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS)
Conclusions on Adherence

- This first analysis of adherence showed a very high detection rate of TFV and FTC in plasma with “on demand” PrEP.
- These results are very encouraging but are not a demonstration of the efficacy of “on demand” PrEP.
- Adherence monitoring will continue during the study to maintain this high level of adherence.
- Interim analysis approved by DSMB and ethics committee based on high adherence and expected efficacy higher than 50%: target 67% efficacy, 32 events, 900 participants.
## Prevention strategies based on ARV

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Country(ies)</th>
<th>Success Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx (2010)</td>
<td>Oral daily Truvada for gay men - Peru, Ecuador, Thailand, Brazil, USA, South Africa</td>
<td></td>
<td>44%</td>
</tr>
<tr>
<td>CAPRISA004 (2010)</td>
<td>Vaginal gel containing 1% Tenofovir in sexually active women</td>
<td></td>
<td>39%</td>
</tr>
<tr>
<td>Partner-PreP study (2011)</td>
<td>Oral daily Tenofovir or Truvada for heterosexual discordant couples - Uganda, Kenya</td>
<td></td>
<td>62% 73%</td>
</tr>
<tr>
<td>TDF2 (2011)</td>
<td>Oral Daily Truvada for heterosexual men or women - Botswana</td>
<td></td>
<td>63%</td>
</tr>
<tr>
<td>VOICE (2011)</td>
<td>Daily use of Vaginal gel with tenofovir or Oral tenofovir or truvada in women – Uganda, South Africa, Zimbabwe</td>
<td></td>
<td>DISCONT. NO EFF.</td>
</tr>
<tr>
<td>Bangkok Tenofovir Study (2013)</td>
<td>Oral daily tenofovir in men or women that injects drugs - Thailand</td>
<td></td>
<td>49%</td>
</tr>
<tr>
<td>ANRS Ipergay</td>
<td>Intermittent Tenofovir in gay men – France, Canada</td>
<td></td>
<td>On going</td>
</tr>
</tbody>
</table>

Truvada approved in Prep by US FDA in July 2012
HIV is now a chronic disease on life-long ART but new problems/questions...

- Persistent inflammation/immune dysfunction
- Subtle but cumulative treatment toxicity
- Clinical aging
- Overburdened health care systems not designed or resourced to provide chronic care
Why it’s time to accelerate HIV cure research now?
A better knowledge on HIV pathogenesis...

- Viral load
- CD4 count (blood)
- Generalized immune activation
- HIV-specific CD8 T cells
- Intestinal CCR5+ CD4+ T memory cells

2-3 weeks: Acute infection
3-10 weeks: Chronic infection
> 6 months: Generalized immune activation

Set points (predictive of progression)
Viral reservoirs & replication
Inflammation & immune activation
**Better knowledge of drivers of chronic activation**

- HIV replication
- HIV proteins (Nef, Tat, Vpx, ..)
- Loss of regulatory cells
- Altered balance of CD4+ T cell subset
- Inflammation
  - ↑ Monocyte activation
  - ↑ T cell activation
  - Dyslipidemia
  - Hypercoagulation
- Co-morbidities
  - Aging
- HIV-associated fat
  - Metabolic syndrome
- CMV
  - Excess pathogens
- Gut Damage =>
  - Microbial translocation

Steven Deeks, IAS 2013
Prospects for achieving sterilizing or functional cure of HIV infection

Actions sur les Modifications épigénétiques :
Histone hypoacetylation
Histone methylation
Methylation de l’ADN

Inhibiteurs d’HDACs
SAHA
Acide valproique
Chaetocine
5-aza-dc

Levée de la Séquestration des facteurs transcriptionnels cellulaires

Inhibiteurs des miRNA antisens
siARN spécifiques

Levée du Blocage de la transcription par les miARN

Levée de l’Inhibition de l’élongation par la RNA polymérase II avec levée de la séquestration de P-TEFb

Levée de la Séquestration des facteurs transcriptionnels cellulaires

Activateurs de la PKC
Bryostatine
Prostratine

Collaboration with Carine Van Lint
2020 A DREAM!

• HCV CURE

• HIV CURE?

• HBV CURE?
Back UP
Global number of people living with HIV & HIV-related deaths: Changes post-2005

2,1 M PLWH in 2013: 38% reduction since 2001
4,2 millions death avoided thanks to ARVs!

“Test & Treat early”… Treatment is prevention!

Source: UNAIDS Global Report 2014
Why do we need a Cure? PLWH Expectations..

2011 workshop on HIV persistence in St Marteen, Fred Verdult asked Steve Deeks why is it important to cure HIV. The answer of Deeks: «life expectancy, long term side effects, financial reasons ».

Fred Verdult (Volle Maan) conducted a survey on 458 PLWHIV in May 2012 presented at HIV Cure symposium in Washington in July:
72% thought it is was very important for them to be cured
When asked what are the most disadvantages of HIV many replied about medical issues but also not having to be anxious about the future anymore, not having to deal with stigma anymore, not being afraid of infect others anymore
Why do we need lifelong ART?
HIV infection persists on ART....

Barriers to HIV Cure
- Latently infected T-cells
- Residual viral replication related to inflammation/immune activation
- Anatomical reservoirs
- ARV penetration into tissues

Palmer et al., Proc Natl Acad Sci U S A. 2008;105:3879-84
Maldarelli et al., Plos Pathogens 2007; 3:484
HIV treatment cascade: Australia 2014

- Living with HIV: 26,000
- Diagnosed: 23,000
- Linked to care: 22,000
- Retained in care: 22,000
- Receiving ART: 18,000
- Suppressed virus: 6,000

% of people living with HIV:
- Numbers of people: 0-35,000
- % of people receiving ART: 0-120%
Transmission

**Treatment Cascade Indonesia: HIV care 2011-2012**

- **PLHIV**: 421000
- **Enrolled in care**: 118343
- **Eligible for ART**: 80039
- **Ever received ART**: 58328
- **Still on ART**: 31002

AIDS data hub, UNAIDS
# Antiretroviral Therapy

## ART eligibility: 5 policy scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>CD4 Cut-off</th>
<th>Recommendations</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>CD4 ≤ 200</td>
<td>Recommended since 2002</td>
</tr>
<tr>
<td>2</td>
<td>CD4 ≤ 350</td>
<td>Recommended since 2010</td>
</tr>
<tr>
<td>3</td>
<td>CD4 ≤ 350 + TasP</td>
<td>Incremental approach 2012</td>
</tr>
<tr>
<td>4</td>
<td>CD4 ≤ 500</td>
<td>Recommended since 2013</td>
</tr>
<tr>
<td>5</td>
<td>All HIV+</td>
<td>“Test and treat”</td>
</tr>
</tbody>
</table>

### Estimated millions of people eligible for ART in LMIC in 2011

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
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<td>11</td>
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<td>32</td>
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</table>
GFHTM: contributions 2002-2013 ($m)
GSK744 LA for PrEP

- Integrase strand-transfer inhibitor analog of dolutegravir
- Formulated as a long-acting nanosuspension for injection (GSK744 LA)
  - Monthly or less frequent injections (12 weeks) maintains plasma drug levels well above 4xPA IC\(_{90}\) in humans
- Interest in GSK744 LA for PrEP; planned Phase II safety and tolerability studies (HPTN 077 and ViiV sponsored protocol 201120)
- Protected macaques from repeated rectal SHIV challenges (Andrews, CROI 2013 and 2014)
- No macaque data on vaginal efficacy to inform PrEP in women
Cohort PRIMO: HIV-DNA decrease
327 patients on HAART, 1305 samples, 3 slope mixt model

Earliness = 2 mois
Earliness = 1.5 mois
Earliness = 1 mois
Earliness = 0.5 mois

Time from treatment initiation

Laanani, Ghosn 2014
ANRS 147 OPTIPRIM: Study design

Primary end-point: HIV-DNA level at M24

Treatment interruption

VISCONTI

0 M24 M30

Co-enrollment: Cohorte CO6 PRIMO

Secondary Endpoints

- **Virologic**: HIV-DNA and HIV-RNA kinetics
- **Immunologic**: CD4 and CD4/CD8 changes
- **Tolerance**: 5 drugs or 3 drugs
- **Pathophysiological studies**: including
  - HIV-RNA in semen and Rectal HIV-DNA biopsy
  - Innate and HIV specific immunity
Cascade de la prise en charge en France en 2010 par groupe de transmission.

Succès actuels

• Maintien dans le soin
  –94% (médiane, intervalle interquartile : 80-100) (au moins une mesure des CD4 tous les 6 mois, évaluée avec FHDH ANRS CO4)

• Couverture du traitement ARV
  –87% des patients sous ARV en 2011; 81% des patients sous ARV (>6 mois)
  –Mise sous traitement rapide après diagnostic

• Charge virale indétectable
  –89% des personnes traitées ont une CV indétectable (<50 copies/ml) en 2011 et 96% avec une CV <500 copies/ml
IPERGAY Study Design

Effectiveness of “on demand” PrEP
Randomized placebo-controlled trial

• High risk MSM
• Condomless anal sex with >2 partners

Full prevention services *
TDF/FTC before and after sex (n = 950)

Full prevention services *
placebo before and after sex (n = 950)

• Counseling, testing for STI, condoms, vaccination, PEP

Primary endpoint: HIV infection
Incidence of HIV infection: 3/100 PY, 50% efficacy, ~ 2000 pts

www.ipergay.fr
Temprano trial overview

Main objective: To assess the benefits and risks of starting ART immediately and/or to receive a 6-month IPT among HIV-infected adults with CD4 counts <800mm$^3$ and no criteria for starting ART immediately according to the most recent WHO guidelines

Location: 9 clinics in Abidjan, Côte d'Ivoire

Methods: randomized 2x2 factorial superiority trial

Main Inclusion criteria
- CD4<800/mm³
- no WHO criteria for starting ART
- & no active TB

Main Outcome
- Death, or
- Severe HIV morbidity

N= 2076 (519 per arm)

Randomization

No drug

ART when WHO starting criteria are met

INH, 6 months

ART when WHO starting criteria are met

Immediate ART

Immediate ART + INH, 6 months

30 months

http://mereva.net/temprano

http://clinicaltrials.gov/ct2/show/NCT00495651
ANRS 12 249 TasP
A cluster-randomised community-based trial of treatment-as-prevention in rural KwaZulu-Natal, South Africa

Francois Dabis (University of Bordeaux)
Marie-Louise Newell (University of Southampton)
Deenan Pillay (Africa Centre, UKZN)
To directly estimate the effect of a universal Test and Treat approach i.e. ART initiated immediately after the diagnosis of infection and irrespective of CD4 count in people not yet eligible for ART on the incidence of HIV infection in the general population in the same setting
Cluster-randomised controlled trial

**Component 1**: Full prevention and HIV testing strategy in both the intervention and control arms

- Current range of community and clinic HIV testing options AND
- Implementation of regular (6 months, then 4 months) rounds of home-based HIV testing
- Comprehensive set of preventive services:
  - IEC, condom distribution, circumcision services. Syndromic management of STIs
TasP trial design (2/2)

Component 2: For all HIV-infected adult individuals identified:

**Control Arm**
- Offer ART according to national guidelines
  - All patients with CD4 <350 cells/mm$^3$, WHO clinical stage 3 or 4 or MDR/XDR TB

**Intervention Arm**
- Offer universal immediate ART initiation
More than 30 years ago: Alarming signals of an emerging epidemic

MS Gottlieb, HM Schanker, PT Fan, A Saxon, JD Weisman.

June 5, 1981 / Vol. 30/ No. 21

Epidemiologic Notes and Reports

Pneumocystis Pneumonia --- Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed Pneumocystis carinii pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

Kaposi's Sarcoma and Pneumocystis Pneumonia
Among Homosexual Men — New York City and California

During the past 30 months, Kaposi's sarcoma (KS), an uncommonly reported malignancy in the United States, has been diagnosed in 26 homosexual men (20 in New York City [NYC]; 6 in California). The 26 patients range in age from 26-51 years (mean 39 years). Eight of these patients died (7 in NYC, 1 in California)—all 8 within 24 months after KS was diagnosed. The diagnoses in all 26 cases were based on histopathological examination of skin lesions, lymph nodes, or tumor in other organs. Twenty-five of the 26 patients were white, 1 was black. Presenting complaints from 20 of these patients are shown in Table 1.

Mobilization of virologists by epidemiologists and clinicians
Why do we need novel therapeutic strategies?

• 35 millions PLWH: only 13 millions on cART
  - Only very few countries with >80% coverage
  - New WHO recommendations = 28 millions eligible

• Lifelong cART:
  - Substantial stigma and discrimination
  - Fears
  - Difficult adherence
  - Toxicity
  - Life expectancy reduced
  - Still a significant morbidity
  - Long term cost

• Treating is preventing HIV infection…

Lifelong cART for all is unlikely to be sustainable…