Outline

Key Pathogenesis elements for ART

Strategies Beyond guidelines

Future drugs and strategies

Antiretroviral Treatment Strategies

Part 2
A success story of research
But a story far from being achieved

- Viral suppression > 90%
- Better ARV drugs
- Simplified treatment
- Quasi Normalized life span
- Transmission reduced

- A unique infection with no vaccine
- No cure  No remission  vaccine
- Long life therapy
- Persistance of immune activation
- Comorbidities
- Cost ; ART accessibility
HIV
A disease of immune activation and inflammation

HIV replication induces immune activation
Immune activation induces inflammation
  immune exhaustion
  immune suppression
Inflammation induced comorbidities
Inflammation
↑ Monocyte activation
↑ T cell activation
Dyslipidemia
Hypercoagulation

Syndrome métabolique

HIV production

Perte de régulation CD4

Translocation microbienne

Coinfections CMV HBV HCV

Co-morbidités Vieillissement

From S Deeks 2013

Persistance d'une inflammation malgré la suppression virale
Pathogenesis of HIV

HIV is deleterious by immune suppression and activation

- Immune activation
  - Inflammation
  - Cardiovascular risk
  - Bone
  - Cognitive disorders
- Immune deficit
  - HBV/HCV
  - Cancers
- Accelerated aging
  - Cancers
- AIDS
  - Cancers

HIV is deleterious by immune suppression and activation.
Time of ART initiation: a key element in reservoir establishment

Plasma viremia

HIV reservoir = residual HIV infection
With HIV DNA integrated in memory CD4
Evolution of HIV RNA and HIV DNA in patients following ART initiation

HIV reservoirs differs from cohorts patients

Lewin and Rouzioux, Review, AIDS 2011

Primary infection
Ghosn, JAC 2010

Early infection
Rouzioux, JID 2005

Elite controllers
Martinez, JID 2008

ART/PI
Hocqueloux 2010

PRIMO inclusion
SEROCO inclusion
ALT
HIC
Visconti
Cumulative Viral load is predictive of mortality under ART

- Observationnal study
- ART Cohort Collaboration
- 33,563 pts
- Estimated cumulative viremia (copies – years)
- After adjustment on age, gender, transmission, BL HIV RNA

Persistant quantitative viremia is predictive of
  - All-cause mortality
  - AIDS-related mortality

Hazard of All-Cause Mortality by Viremia Copy-Yrs Deciles (Controlling for Cross-sectional VL)

Earliest control of HIV replication is the best way to preserve future

- **Nadir of CD4** is a predictor for death; morbidity (CVasc); cancer; ART failure
- **Above 500 CD4** is the optimal way to preserve clinical future
- **ART at PI**:
  - Limitation of viral set point
  - Reservoir size limitation
  - Normalized immune activation
HPTN 052

Essai randomisé

**1763** HIV couples hétéro sérodifférents avec entre 350 et 550 CD4

Preservatif recommandé
Afrique ++/ Asie
ART immédiat vs ART différé
96% suppression viro

Transmission : 1 vs 27
96% réduction transmission

Beatriz Grinsztejn et al.
*Lancet Infect Dis* 2014;14: 281–90

PARTNER

• Etude observationnelle europe

• **767 couples** sérodifférents (homo masculins et hétéro)
  Rapports occasionnels non protégés
  Pas d’utilisation de PEP ni de PrEP

• Après 894 couple-années de suivi et med 15 000 RS non protégées
  **Transmission : 0**
  Suivi nécessaire / ET du %

Rodger A, *CROI 2014, Abs. 153LB*
Antiretroviral therapy

- A highly effective therapy
- A highly effective prevention

...A « double hit strategy »
Goals of Antiretroviral Therapy

- Reduce HIV-associated morbidity and prolong duration and quality of survival
- Restore and preserve immunologic function: > 500 CD4; normalize CD4/CD8
- Maximally and durably suppress HIV-1 RNA
  - Persistently below level of detection (< 20-75 copies/mL, depending on the assay used)
  - Isolated “blips” not uncommon in successfully treated patients and not thought to predict virologic failure
- Prevent HIV transmission
- Decrease maximally reservoirs

DHHS Guidelines for Antiretroviral Therapy in Adults and Adolescents. March 2012.
Viral replication has to maximally suppressed Ideally in the shortest time

Maximal suppression of HIV required to
- Prevent disease progression
- Decrease immune activation
- Prevent resistance

Target VL below detection

- W4 : -2 log decrease in HIV RNA
- W12 : < 400 cp/ml
- W24 : > 50 cp/ml

In BL high VL .. Full suppression may require longer time
How to best manage HIV patient?

1. Initiation
2. Virologic suppression
3. Treatment Failure

HIV therapy = a long life therapy
# Antirétroviraux : 2014

<table>
<thead>
<tr>
<th>NRTI</th>
<th>NNRTI</th>
<th>Protease</th>
<th>Inhib Integrase</th>
<th>CCR5</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF</td>
<td>Nevirapine</td>
<td>Lopinavir</td>
<td>Raltegravir</td>
<td>Maraviroc</td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>Efavirenz$^6$</td>
<td>Atazanavir</td>
<td>Elvitegravir</td>
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</tr>
<tr>
<td>ABC</td>
<td>Rilpivirine</td>
<td>Darunavir</td>
<td>Dolutegravir</td>
<td></td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>Etravirine</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3TC/FTC</td>
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</table>

**Combinaisons fixes**
- TDF/FTC/EFV
- TDF/FTC/RPV
- TDF/FTC/cobi/EVG ...

- Malgré puissance et simplicité des combos fixes
- Standard ART est toujours une trithérapie

**Innovation nécessaire**
Reasons to individualize ART

- Reduce drug burden
- Prevent / reduce long term toxicity
- Spare drug capital
  Adapt ART to CD4 and plasma VL and to reservoirs?
- Cost reduction
Can we initiate a “non triple” ART?

**Induction**
- Nb drugs is function
  - HIV RNA
  - CD4
  - Drug potency
  - Robustness
  - HIV DNA ?

**1996 Triple drug ART:** a revolution
- More potent drugs
- More robust drugs
- Earlier initiation with lower VL and higher CD4

**2014**
- Monotherapy
- Dual therapy
- Reduced dosages

**Which strategies?**
**GARDEL: Dual ART LPV/r +3TC**
Non inferior to Triple ART in ART naïve patients

Phase III, randomized, controlled, open-label study
Argentina, Chile, Mexico, Peru, Spain, US.

<table>
<thead>
<tr>
<th>HIV-1 RNA &lt; 50 W48</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT exposed - Snapshot</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>LPV/r 400/100mg BID + 3TC 150 mg BID</td>
</tr>
<tr>
<td>n=217</td>
</tr>
<tr>
<td>LPV/r 400/100mg BID + 3TC /FTC + NRTI</td>
</tr>
<tr>
<td>n=209</td>
</tr>
</tbody>
</table>

426 ART- naïve pts
VL: 4.87 log
CD4: 320/mm3
No PI resistance

- Grade 2-3 adverse events more frequent in triple-ART arm (88 vs 65 events)
- Hyperlipidemia more common in dual-ART arm (23 vs 16 pts)
- Limited resistance (2 with M184V in LPV/3TC)

*Cahn P, et al. EACS 2013. Abstract LBPS7/6*
NEAT-001/ANRS 143: DRV/RTV + RAL vs DRV/RTV + TDF/FTC in Naive Pts

- Randomized, open-label, phase III study

- 805 ART naive patients
- CD4: 345/mm³
- CV: 4.76 log
- > 100 000 cp/ml: 35%

```
DRV/RTV 800/100 mg QD + RAL 400 mg BID (n = 401)
```

```
DRV/RTV 800/100 mg QD + TDF/FTC 300/200 mg QD (n = 404)
```

- **Primary endpoint**
  - **Virologic**: Change of treatment before Wk 32 because of insufficient response or HIV-1 RNA ≥ 50 c/mL at Wk 32 or beyond
  - **Clinical**: Death, any new AIDS-defining event, any new non-AIDS event

NEAT: RAL + DRV/RTV Noninferior to TDF/FTC + DRV/RTV at 96 Wks

- Overall, regimens noninferior by % reaching composite primary endpoint of 6 virologic and clinical endpoints at Wk 96
  - RAL: 17.4%; TDF/FTC: 13.7%
  - Inferior response in pts with BL CD4+ < 200 and a trend toward more primary endpoints in pts with BL VL ≥ 100K

- PBV (RAL: n = 66; TDF/FTC: n = 52)

- No pts with resistance in TDF/FTC arm vs 5 with integrase mutations and 1 with K65R

  No difference in terms of efficacy

  When CD4 are low or VL high prefer triple ART

<table>
<thead>
<tr>
<th></th>
<th>RAL</th>
<th>TDF/FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BL HIV-1 RNA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 100,000 c/mL</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>≥ 100,000 c/mL</td>
<td>36</td>
<td>27</td>
</tr>
<tr>
<td><em>P</em> = .09</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

  | **BL CD4+ cell count** |        |         |
  | < 200/mm³           | 39.0   | 13.6    |
  | ≥ 200/mm³           | 21.3   | 12.2    |
  | *P* = .02           |        |         |

- **Significantly greater mean increases in fasting lipids in RAL arm**

MODERN Study Wk 48 Results:
DRV/RTV + MVC Inferior to DRV/RTV + TDF/FTC

Noninferiority Margin (95% CI)
-10% (-17.7% to -6.1%)

HIV-1 RNA <50 c/mL (%)

Virologic Failures
- DRV/RTV + MVC, n=38
- DRV/RTV + TDF/FTC, n=13

Study terminated early due to inferior efficacy
October 4, 2013, following Data Monitoring Committee recommendation

MODERN Study (A4001095 Early Termination Investigator Letter).
ClinicalTrials.gov. NCT01345630.
Alternative trithérapie

EFV 400-mg non inférieur à 600-mg EFV combiné à TDF/FTC en 1° ligne

- Etude noninfériorité randomisée, double aveugle versus placebo

<table>
<thead>
<tr>
<th>HIV-1 RNA &lt; 200 cp/ml S48</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC=F</td>
</tr>
<tr>
<td>ITT</td>
</tr>
<tr>
<td>PP</td>
</tr>
<tr>
<td>90.0 %</td>
</tr>
<tr>
<td>94.1 %</td>
</tr>
<tr>
<td>98.3 %</td>
</tr>
<tr>
<td>85.8 %</td>
</tr>
<tr>
<td>92.2 %</td>
</tr>
<tr>
<td>97.4 %</td>
</tr>
</tbody>
</table>

EFV* 400 mg + Placebo + TDF/FTC n = 324

EFV* 600 mg + TDF/FTC n = 312

636 ART-naive
CD4 : 273 /mm³
HIV-1 RNA : 4.75 log

- Effets secondaires plus fréquents avec EFV 600 47.2% mg vs EFV 400 mg 36.8%; p=.008

- Arrêts traitements plus fréquents avec EFV 600 mg (intolérance) vs EFV 400 mg 1.9% vs 5.8%; p = .010
Who are the patients with VL < 50 cp/ml with mono LPV/r V / r?

Patients with lower HIV DNA 3.16 vs 2.87 log HIV DNA
Etude pilote de bithérapie NRTI en initiation chez des patients avec CD4 élevés et CV faible

- 20 patients
- CV < 30 000 cp/ml  
  Med : 10.395 cp
- CD4 > 350/mm³  
  Med : 592
- Initiation avec 2 NRTI  
  TDF/FTC : 19  
  ABC/3TC : 1

Délai d’indétectabilité < 50 cp/mL = 4 [4-12] semaines

Seang Katlama 2014 JAC in press
Individualize ART for a long life therapy

**Initiation = Induction**

**Maintenance therapy**

- **Daily treatment**
  - robust monotherapy PI
  - Bitherapy
  - Triple ART with reduced dosage
  - Intermittent therapy

**Objectives**

Virological suppression
CD4 > 500 et CD4/CD8 > 1
Low DNA reservoir
MONET: Primary Efficacy Analysis: HIV RNA <50 copies/mL at Week 48

<table>
<thead>
<tr>
<th></th>
<th>Per Protocol analysis (PP)</th>
<th>Intent to Treat analysis (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary analysis</td>
<td></td>
</tr>
<tr>
<td>HIV RNA &lt;50 by Week 48 (%)</td>
<td><strong>87.8%</strong></td>
<td><strong>85.3%</strong></td>
</tr>
<tr>
<td></td>
<td><strong>86.2%</strong></td>
<td><strong>84.3%</strong></td>
</tr>
<tr>
<td></td>
<td><strong>-1.6%; lower limit 95% CI: -10.1%</strong></td>
<td><strong>-1%; lower limit 95% CI: -9.9%</strong></td>
</tr>
<tr>
<td></td>
<td><strong>86.2%</strong></td>
<td><strong>84.3%</strong></td>
</tr>
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</table>

J. Arribas et al, AIDS 2010
Qui sont les patients maintenant CV < 50 cp/ml sous DRV/r ?

Les patient avec CV ultrabasse et ADN faible

**Response**

<table>
<thead>
<tr>
<th>Response</th>
<th>Difference (Lower limit CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx success (PP, n=204)</td>
<td>- 4.9% (-9%)</td>
</tr>
<tr>
<td>Rx success (ITT, n=225)</td>
<td>- 4.5% (-11%)</td>
</tr>
</tbody>
</table>

-9% > -10% → mono DRV/r non inferior to DRV/r + 2 NRTIs

-11% < -10% → failure to demonstrate non-inferiority
PI/r monotherapy
Monotherapy with LPV/r*1

MONARK
Initial therapy

M03-613
Induction/Maintenance

OK04
Simplification

Patients (%)

0 16 32 48 60 80 100

0 16 32 48 64 80 96

0 12 24 36 48

MONARK
NAÏVE

M03-613
SUPPRESSED (SHORT†)

OK04
SUPPRESSED (LONG‡)

Discontinued
On study, HIV-1 RNA >400 copies/mL
On study, HIV-1 RNA 50–400 copies/mL
On study, HIV-1 RNA <50 copies/mL

*Boosted PI monotherapy is an off-label approach.
†Short-term suppression: ≤24 weeks;‡Long-term suppression: >6 months.3

Switching therapy

- **Objective**: maintain viral suppression
- Decrease drug burden
- Decrease/prevent toxicity
- Simple regimen
- Robust regimen

- Reconstitutes ART and resistance history
- Take into consideration BL characteristics and time of viral suppression
- The switched regimen has to include potent and robust drug(s)
- Do not keep resistant drugs that cumulates toxicity and cost
Can we reduce drug burden?

- Monothérapie
  - IP
  - molécule robuste ..DTG ?

- ARV intermittent
  - Essai 4D ANRS

- Bithérapies
  - Inhibiteur intégrase
  - NRTI       ETRAL ANRS

- Réduction dose
  - IP boosté
  - NNRTI
## New drugs

- High potency
- High tolerability
- Coformulable
- Long half life
- High genetic barrier to resistance
- Low production cost

- To reduce
  - Nb intakes
  - Need for monitoring
  - Delivery optimization

### Drugs in clinical development

<table>
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<tr>
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<th>NRTI</th>
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<th>CCR5</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAF</td>
<td>LPA 278</td>
<td>GS 744</td>
<td>LPA GS 744</td>
<td>Cenicri viroc</td>
</tr>
<tr>
<td>NRTI BMS</td>
<td>MK-1439</td>
<td></td>
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</tbody>
</table>
Dolutegravir
*a major drug in ARV armentorium*

- **High potency**
  - $2.6 \log_{10} \text{cp/mL}$ in 10 days
  - *Superior to* EFV et darunavir/r in naïve patients
  - *non-inferieur à* raltegravir in naïve patients
  - *Supérieur à* raltegravir inpretreated (INI naive)
  - Active in 63% patients failing INI

*High genetic barrier to resistance*

**Once daily** ($t_{1/2} = 15 \text{ h}$) **Low dosage** (50 mg)

- **Limited PK variability /drug drug interactions**
  - No CYP induction or inhibition
    - **Excellent tolerability**

- **Low production cost**
Tenofovir Alafenamide Fumarate (TAF) a new version of an old drug

- Prodrogue NRTI, converted in active tenofovir diphosphate
- Different du tenofovir disoproxil fumarate (TDF Viread®)
  - More active than TDF, 300% plus ACT VL reduction or 1.5 log vs 1.0 log
  - Higher intracellular concentration ++ less in plasma
- Better tolerated kidney and bones
- Co-formulation possible
- Dosage: 10 mg par jour
New long acting antiretroviral drugs
A major option for treatment and prevention

**Rilpivirine LA**
- Nanosuspension NNRTI
- Injections IM monthly

**GSK744 LAP**
- Nanosuspension integrase inhibitor
- IM and SC /month or /3 months
  200-1200 mg tested

**GSK 744 oral** (Etude Latte)
10 20 30 60 mg + TDF/FTC
Efficacy : > 90%
No difference between doses

Margolis et al. CROI 2014; Boston, MA. Abstract 91LB.
Antiretroviral Strategies

- Treat HIV as ART normalized survival and prevent partner’s transmission
- ART normalizes life of a person living with HIV
- Earlier treatment with better drugs
- Triple drug is the rule particularly for patients with high viral loads
- Individualized treatment will allow to adjust to each patient history
- Saving drugs is key to preserve ART options
Why do we need a Cure for HIV?

➢ To control the HIV pandemics

How?

Current AntiRetroVirals

Reduce drug burden

Persistence of HIV Reservoirs

NO AIDS

Can we decrease the HIV reservoirs and stop ART? Functional Cure?

or eradicate HIV Sterilizing Cure?
Is Cure achievable?

**Elite controllers**

Never treated

**Special phenotype:**
HLA /Strong CD4 and CD8 response/High level cytokine towards HIV/Preserved central memory cells/Low immune activation

**Berlin patient:** CCR5 defective stem cell graft

- **Mississipi baby**
- **Visconti patients**
  - Treated at early stage of infection
- **Chronic long term patients? Salto**
SALTO ANRS 116
Treatment interruption in early treated patients
with CD4 > 350 and VL < 50 000 cp/ml

95 patients
- Age 40 years (IQR: 36–45).
- Pre-cART values
  CD4 : 454 /mL (392–576)
  VL : 4.3 log_{10} cp/ml (3.9 – 4.5)
  CD4 nadir : 382 /mL (340–492).
- Duration of cART : 5.3 years (4.0–6.0)-
- Baseline values
  CD4 count : 813 cells/mL (695–988),
  DNA : 206 copies/10^6 PBMCs
  (IQR: 53–556)

12 months post TI
- 7/95 patients still had a VL<400 cp/ml
  KP: 7.5%, CI: 3.7-14.6)
- 4 kept a VL<400 copies/mL up to 36 months;
- All had CD4 cell >500/mm³
- HIV DNA was the only significant predictor of maintaining VL < 400 cp/ml
  med value : < 10 vs 233 cp /
  10^6 PBMCs p < 0.001

Potential strategies to reduce HIV reservoirs

Maraviroc
Anti-inflammatory drugs
- Statins
- OH-Chlorochin

Massive CD4 T-cell depletion
Bacterial translocation

Systemic Inflammation

Pre-Probiotics

Viral Co-Infections

Antiviral drugs

Immune Activation

ARV Intervention
- Intensification
- Nevirapine

CD8
Cellular Immunity
Immune Intervention
- Anti-HIV vaccine
- IL7

Residual Replication

Gene therapy

HIV Reservoirs Latency

Quiescent T cells activation
- IL7

Pre/post-transcriptional factors disruption
- HDACi
- HMBA

Anti-co-stimulatory molecules
- anti PD1 / anti PDL1
- anti-CTLA4
- anti-CD137

CD4