How to best manage HIV patient?

Treatment Failure

Treatment success

HIV therapy = a long life therapy
Why do we want to change a suppressive ART?

- Side effect
- Comorbidities
- Reduce drug burden
- Simplification
- How to modify ART?
- Reservoir
**Concepts in Induction Maintenance ART**

**Induction**

- Nb drugs required
- Depending on
  - HIV RNA
  - CD4
  - HIV DNA

**Maintenance strategy**

- **Which antiviral potency** do we need
  - to maintain viral suppression
  - CD4 above 500 /mm^3
  - without enlarging reservoir?

- **Which markers can we use?**
  - Viral DNA?
  - Activation markers?
Simplication with drug burden reduction

Newer efficacious and well tolerated ARVs with higher potency and genetic barrier to resistance

Drugs with relatively low potency and genetic barrier to resistance

Monotherapy

Dual Therapy

Triple Therapy

Triple therapy needed to ensure efficacy and limited emergence of resistance

Switching therapy

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

- Reconstitutes ART and resistance history
- The switched regimen has to include potent and robust drugs
- Do not let a drug in a position of functionnal monotherapy
- Do not keep resistant drugs that cumulates toxicity and cost
Modern dual-therapy studies: 48-week results

- **ACTG 5142**: EFV + 2 NRTI (n=250), EFV + LPV/r (n=250), ATV QD + RAL BID (n=63), LPV/r + 2 NRTI (n=253), ATV BID + RAL BID (n=63), ATV/r QD + FTC/TDF (n=60)
- **SPARTAN**: ATV BID + RAL BID (n=105), LPV/r BID + FTC/TDF (n=105), ATV/r QD + FTC/TDF (n=105)
- **PROGRESS ACTG 5262**: ATV/r QD + FTC/TDF (n=112), DRV/r QD + FTC/TDF (n=70), ATV/r QD + MVC QD (n=60)
- **Study 1078**: EFV + 2 NRTI (n=250), EFV + LPV/r (n=250), ATV QD + RAL BID (n=63), LPV/r + 2 NRTI (n=253), ATV BID + RAL BID (n=63), ATV/r QD + FTC/TDF (n=60)

% of patients with HIV-1 RNA <200 copies/mL and <50 copies/mL

Created from:
## Dual therapy

Summary of safety outcomes in studies of dual-therapies in ARV-naïve patients*

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Follow up</th>
<th>Lipids</th>
<th>Renal</th>
<th>Bone</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTG 5142¹</td>
<td>LPV/r + EFV</td>
<td>96 weeks</td>
<td>Elevated</td>
<td>Not reported</td>
<td>Not reported</td>
<td>-</td>
</tr>
<tr>
<td>PROGRESS²</td>
<td>LPV/r + RAL</td>
<td>96 weeks</td>
<td>Elevated</td>
<td>Improved</td>
<td>Improved</td>
<td>CPK ↑</td>
</tr>
<tr>
<td>SPARTAN³</td>
<td>ATV† + RAL</td>
<td>96 weeks</td>
<td>Neutral</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Bilirubin ↑</td>
</tr>
<tr>
<td>ACTG 5262⁴</td>
<td>DRV/r + RAL</td>
<td>48 weeks</td>
<td>Elevated</td>
<td>Not reported</td>
<td>Not reported</td>
<td>-</td>
</tr>
<tr>
<td>Study 1078⁵,⁶</td>
<td>ATV/r + MVC</td>
<td>96 weeks</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Improved</td>
<td>Bilirubin ↑</td>
</tr>
</tbody>
</table>

*Summary of safety outcomes in studies of dual-therapies in ARV-naïve patients*
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

MONARK

MONARK

NAÏVE
SUPPRESSED (SHORT†)
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.²

MONET: Primary Efficacy Analysis: HIV RNA <50 copies/mL at Week 48

**Per Protocol analysis (PP)**
- **Primary analysis**
  - HIV RNA <50 by Week 48 (%): 87.8%
  - 1.6%; lower limit 95%CI: -10.1%

**Intent to Treat analysis (ITT)**
- HIV RNA <50 by Week 48 (%): 85.3%
  - 1%; lower limit 95%CI: -9.9%

J. Arribas et al, AIDS 2010
Who are the patients with VL < 50 cp/ml in DRV/r?

Patients with low VL and low DNA

PP population

- 99.0%

ITT population

- 87.5%

Rx success (PP, n=204))

- 94.1% ± 9% (Lower limit CI)

Rx success (ITT, n=225)

- 92.0% ± 11% (Lower limit CI)

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

-11% < -10% → failure to demonstrate non-inferiority
ENCORE1: 400-mg EFV Noninferior to 600-mg EFV With TDF/FTC for Initial ART

- Randomized, double-blind, placebo-controlled, noninferiority phase III trial
  - Part of ongoing effort to identify ARVs effective at lower doses (and cost)

\[\text{Stratified by clinical site and HIV-1 RNA at screening}
\]
\[\text{(< 100,000 or \geq 100,000 copies/mL)}\]

\begin{align*}
\text{ART-naive pts,} \\
\text{CD4+ 50-500 cells/mm}^3, \\
\text{HIV-1 RNA > 1000 copies/mL} \\
\text{(N = 636)}
\end{align*}

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>(n)</th>
<th>HIV-1 RNA &lt; 200 c/mL at Wk 48, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>000</td>
<td>EFV* 400 mg + placebo + TDF/FTC 300/200 mg</td>
<td>324</td>
<td>90.0</td>
</tr>
<tr>
<td>000</td>
<td>EFV* 600 mg + TDF/FTC 300/200 mg</td>
<td>312</td>
<td>85.8</td>
</tr>
</tbody>
</table>

- No significant difference in SAEs between treatment arms
- More pts with AEs for EFV 600 mg vs EFV 400 mg (47.2% vs 36.8%; \(P = .008\))
- More pts discontinued EFV 600 mg due to AE vs EFV 400 mg (1.9% vs 5.8%; \(P = .010\))

Is HIV cure achievable?
Decrease reservoir
Drug free remission: Functional cure
Drug burden decrease: Reduce ARV

- Eradicate reservoir
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**
Mississippi baby

- Born 35 weeks gestation; mother tested at delivery low VL 2423 cp/ml
- ART started at H31. 13,000 cp/ml up M18 then lost to FU
- M24: functionnal cure

Viral load evolution (c/ml)

HIV RNA: undetectable CV plasmatique indétectable
ELISA negative
HIV DNA: undetectable

Régime ARV 1: ZDV/3TC/NVP (31 heures - 7 jours)
Régime ARV 2: ZDV/3TC/LPV/r (7 jours - 18 mois)
Arrêt des ARV
Visconti Patients
Post ART controllers

- 12 patients treated at PHI
  ART Duration (med): 35mths
  Duration Off ART: 5 years

- **CD4 count**
  - pre ART: 489 (371-955)
  - at ART stop: 931 (354-1639)
  - last value: 837 (388-1598)

- **HIV RNA**
  - preART: 5.0 log (3-7.3)
  - last value: 1.7 log (1.7-2.4)

- After > 6 years OFF ART
  Median RNA: <20 copies/mL
  Median DNA = 83 copies/M PBMC
  Very limited CD8 activation

A. Saez-Cirion et al., # F-126 – CROI 2011 (Boston)
## 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/mm$^3$
- HIV DNA was the only significant predictor of maintaining VL < 400 cp/ml
  - med value : < 10 vs 233 cp / 10$^6$PBMCs $p < 0.001$

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?
Potential strategies to reduce HIV reservoirs

Maraviroc
Anti-inflammatory drugs
- Statins
- OH-Chlorochin

Massive CD4 T-cell depletion
Bacterial translocation

Systemic Inflammation

Pre-Probiotics

ARV Intervention
- Intensification
- Nevirapine

Cellular Immunity
Immune Intervention
- Anti-HIV vaccine
- IL7

Gene therapy

Immune Activation

Viral Co-Infections

Antiviral drugs

Pre/post-transcriptional factors disruption
- HDACi
- HMBA

HIV Reservoirs Latency

Quiescent T cells activation
- IL7

CD8

CD4

CD4

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

Bacterial translocation

Residual Replication

Cellular Immunity

Immune Intervention

Pre/post-transcriptional factors disruption
- HDACi
- HMBA

Gene therapy

Gene therapy

Quiescent T cells activation
- IL7

Cellular Immunity

Immune Intervention

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Gene therapy

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- IL7
Goals of Anti RetroViral Therapy

- Normalized life expectancy
- Normal CD4/CD8
- Minimal Immune Activation/inflammation
- No viral replication
- Minimal HIV Reservoirs
- Prevent HIV Transmission
Need for individualized therapy in Long-term virological suppression

Minimal ART
Maximal viral suppression

Control of HIV
- Plasma
- Compartments
- Reservoirs

Optimal immune status and minimal activation

ART Toxicity
- Cardiovascular risk
- Mitochondrial toxicity
- Bone disorders
- CNS?

AGING
- Cardiovascular risk
- Cancer
- Cognitive disorders
- Renal disorders
HIV is a global challenge
Scientific
Medical
Social
Human rights and dignity
• Test any individual with sexual life
• Early treatment
• Maximal viral suppression
• Restore immunity > 500 CD4
• Treatment as confort for life
• Treatment as a control for epidemics