Advances in Antiretroviral Therapy

Pr Christine Katlama
Sorbonne University Paris VI
Pitié-Salpêtrière Hospital, Paris
Pierre Louis institute
Anti-Retroviral Therapy Achievements
A permanent Evolution and Revolution

- **1986**: AZT first ARV
- **1994**: First AZT prophylaxis of mother to child T
- **1996**: *Triple therapy regimen*: mortality falls down
- **2006**: TASP HPTN052 /partners: \( \text{U} = \text{U} \)
  prevention of transmission from HIV+ to HIV-
- **2015**: *Universal ART* at any CD4
- **2016**: *PrEP* ART can prevent HIV (primary prophylaxis)
Optimization of ART
an evolutive concept over time

- **2000 Ultimate goal was efficacy**
  Improve efficacy even if sacrificing for toxicity and complexity (no choice)

- **2010 Simplify daily regimen**
  With efficacy obtained with many regimens
  Simplification was the new goal
  Switching from from TID to BID and QD

- **2015 Individualized optimization**
  To reduce drug exposure
Treatment as Prevention TasP: No contamination in serodifferent couples

HPTN 052
96% reduced transmissions initially
93% reduction in final analysis:
- 8 transmissions in ART arm
  - 4 virological failures
  - 4 prior to suppression

PARTNER 2
> 75,000 CLSI in 758 MSM serodifferent couples where HIV+ partner on suppressive ART (VL<200)
= ZERO transmission

Universal ART
Unlimited control of viral replication

- To prevent irreversible damages of HIV replication
- To free PLHIV from stress of transmission
- To stop interindividual transmission
- To decrease discrimination linked to fear

A maximal protection for oneself and for others
A message to be more diffused
The best argument for Adherence/testing
Antiretroviral Drugs

- For HIV pos: a highly effective therapy
- For HIV neg: a highly effective prevention

...a double hit strategy to end HIV epidemics
HIV and ART
Where are we in 2019?

Bad news but nothing new
HIV is an integrated virus with persistent replication
• No cure
• No remission
• No therapeutic vaccine
• Rebound of VL after 10 days off ART

Good news
• Durable VS with ART
• No transmission
• No escape in VL if ARV drugs effective
• Long term VS reduced HIV DNA
• Immune restoration

The biggest challenge
Long life suppressive ART over to 6-7 decades
The « undetectable Status »

**How to get there ?**

- Taking ARV drugs
- Taking the right drugs
- On ART as earlier as possible as lower is
  - HIV RNA and DNA
  - immunity prejudice
  - better will be immune reconstitution

**How to remain life long suppressed?**

- Compliance
- Education
- Patient empowerment
- Acces to viral monitoring
- Health care worker empathy
- Fight against stigma
- Long acting ART regimen
### When to ART?

A worldwide consensus

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAS-USA¹</td>
<td>Initiate ART as soon as possible after HIV diagnosis. Rapid start (including same day) unless patient not ready to commit.</td>
</tr>
<tr>
<td>DHHS²</td>
<td>ART recommended for all regardless of CD4 T lymphocyte count. Therapy should be initiated as soon as possible.</td>
</tr>
<tr>
<td>OMS³</td>
<td>Start ART in all regardless of WHO clinical stage or CD4. Prioritise severe/advance clinical disease (WHO stage 3 or 4) and adults with CD4 ( \leq 350 )</td>
</tr>
<tr>
<td>EACS⁴</td>
<td>ART should always be recommended irrespective of the CD4 count. Immediate (same day ART) should be considered in certain situations.</td>
</tr>
</tbody>
</table>

1. Saag M et al, JAMA, 2018
3. [http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf](http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf)
Starting ART early is beneficial

Meta-analysis

✓ Increased number of people starting ART within 90 days (Relative Effect 1.43)

✓ Increased viral suppression (Relative Effect of 1.18)

✓ Decreased Lost to FU (Relative effect of 0.65)

✓ Trend towards decreased mortality (relative effect of 0.47) and late return (relative effect of 0.85)

CASCADE: Same day ART initiation versus SOC in Home-based Testing program Lesotho

12-month viral suppression 50 vs 34%

12-months viral suppression

Labhardt ND et al. JAMA 2018; 319(11):1103-12
# Antiretroviral Drugs 2019

<table>
<thead>
<tr>
<th>NRTI</th>
<th>NNRTI</th>
<th>Protease Inhibitors</th>
<th>Integrase Inhibitors</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF</td>
<td>Nevirapine</td>
<td>Lopinavir</td>
<td>Raltegravir</td>
<td>Maraviroc</td>
</tr>
<tr>
<td>TAF</td>
<td>Efavirenz</td>
<td>Atazanavir</td>
<td>Elvitegravir</td>
<td>Enfuvirtide</td>
</tr>
<tr>
<td>ABC</td>
<td>Rilpivirine</td>
<td>Darunavir</td>
<td>Dolutegravir</td>
<td>Ibalizumab</td>
</tr>
<tr>
<td>3TC/FTC</td>
<td>Etravirine</td>
<td>Doravirine</td>
<td>Bictegravir</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Single Tablet regimen</th>
<th>3-DR</th>
<th>STR</th>
<th>2-DR</th>
<th>2-DR</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC/EFV Atripla R</td>
<td>TDF/FTC/ RPV Eviplera R</td>
<td>TDF/FTC/ EVG/ c Stribild R</td>
<td>TAF/FTC/ EVG/ c Genvoya R</td>
<td>ABC/3TC/DTG Trumeq R</td>
</tr>
<tr>
<td>TDF/FTC/EVG/c Stribild R</td>
<td>TAF/FTC/ EVG/ c Genvoya R</td>
<td>ABC/3TC/DTG Trumeq R</td>
<td>TAF/FTC/ BIC Bictarvy R</td>
<td>DOR/TDF/3TC Delstrigo R</td>
</tr>
</tbody>
</table>

- **2-DR**
  - DTG/RPV Juluca R
  - DTG / 3TC Dovato R
**Bictégravir**

un inhibiteur d’intégrase combiné à TAF/FTC

**Essai GS 1489**

- Patients naïfs
- BIC/TAF/FTC n=314
- DTG/ABC/3TC n=315
- ARN VIH : 4.4 log10
- CD4: 450/mm³

**Essai non infériorité**

% ARN VIH < 50 c/ml (borne inférieure de l’IC 95 % de la différence = - 12 %,

Pas de différence tolérance clinique, osseuse, rénale

<table>
<thead>
<tr>
<th>ARN VIH &lt; 50 c/ml (PP)</th>
<th>ARN VIH ≥ 50 c/ml</th>
<th>Pas de donnée virologique</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIC/F/TAF : 99,3 %</td>
<td>1,0</td>
<td>6,7</td>
</tr>
<tr>
<td>DTG/ABC/3TC : 98,6 %</td>
<td>2,5</td>
<td>4,4</td>
</tr>
</tbody>
</table>

**Echec CV > 200 c/ml**

- BIC/FTC/TAF (1) ; DTG/3TC/ABC (4)

aucune résistance détectée

Gallant J. Lancet. 2017 :2063-2072
Doravine

- NNRTI 2d generation
- active on the most frequent NNRTI mutations
- Once daily; no food constraints
- Limited drug interactions +++  Tolerability >>>> EFV CNS and lipides

**DRIVE FORWARD** DOR vs DRV

766 naive patients  
CV : 4.35 log_{10} CD4 : 435/mm^3

**DRIVE AHEAD** DOR vs EFV

680 naive patients  
CV:4.4 log_{10} CD4 : 435/mm^3

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>DOR/3TC/TDF</th>
<th>EFV/FTC/TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>84%</td>
<td>81%</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
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<tr>
<td>24</td>
<td></td>
<td></td>
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<tr>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td></td>
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</tr>
</tbody>
</table>

Différence : 3,5 %  
(IC 95 % : - 2,0 à 9,0)

Squires KE, IAS 2017, Abs. TUAB0104LB

† FDA Snapshot Approac
EfDA MK-8591

- transcription and translocation
- NRTTI
- 4 Ethynil fluoro deoxyadenosine
- Fluor : favors liposolubility and et intracellular C i
- Potent antirétroviral ++
- \( C_{50} : 1.5 \text{nM} \)
- No drug interactions
- Long half life +++ 120 h
- Potential flexible dosing of once daily, once weekly and less
- High concentration in genital tract
- Promising drug in treatment and prevention

**Réduction CV (log\(_{10}\) c/ml)**

**Dose MK-8591**
- 0.5 mg
- 1 mg
- 2 mg
- 10 mg
- 30 mg

**Jours**
Islatravir and doravirine dual therapy
Phase 2 MK-8591 011 – Results W48

- **5 rebonds** entre 50 et 200 c/ml (2 dans bras 0,25 mg, 2 dans bras 0,75 mg, 1 dans bras TDF) mais tous avec CV de confirmation < 80 c/ml
- **Evolution moyenne CD4 S0-S48** : ISL toutes doses combinées : + 166/mm³, DOR/3TC/TDF : + 195/mm³
- **Arrêts pour événement indésirable** : 2 dans le bras ISL 2,25 mg (diarrhée/vomissements après J200, réactivation VHB) et 1 dans le bras DOR/3TC/TDF (aggravation de syndrome de QT long congénital)

**Virological results**

<table>
<thead>
<tr>
<th>CV &lt; 50 c/ml</th>
<th>CV ≥ 50 c/ml</th>
<th>Pas de donnée virologique</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISL (0,25 mg) + DOR (n = 29)</td>
<td>89,7</td>
<td>6,9</td>
</tr>
<tr>
<td>ISL (0,75 mg) + DOR (n = 30)</td>
<td>90</td>
<td>6,7</td>
</tr>
<tr>
<td>ISL (2,25 mg) + DOR (n = 31)</td>
<td>83,9</td>
<td>12,9</td>
</tr>
<tr>
<td>DOR/3TC/TDF qd (n = 31)</td>
<td>77,4</td>
<td>6,5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CV &lt; 50 c/ml</th>
<th>CV ≥ 50 c/ml</th>
<th>Pas de donnée virologique</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISL (0,25 mg) + DOR (n = 28)</td>
<td>89,3</td>
<td>7,1</td>
</tr>
<tr>
<td>ISL (0,75 mg) + DOR (n = 30)</td>
<td>90</td>
<td>6,7</td>
</tr>
<tr>
<td>ISL (2,25 mg) + DOR (n = 27)</td>
<td>88,9</td>
<td>3,7</td>
</tr>
<tr>
<td>DOR/3TC/TDF qd (n = 28)</td>
<td>96,4</td>
<td>3,6</td>
</tr>
</tbody>
</table>
ATLAS and FLAIR:
Long-Acting Injectable CAB + RPV vs Daily Oral Three-Drug ART

- Multicenter, randomized, open-label phase III noninferiority trials

**Day 0**
- CAB 30 mg + RPV 25 mg PO QD (n = 308)
- LA CAB 400 mg + RPV 600 mg IM Q4W (n = 303)
- Continue Baseline ART PO (n = 308)

**Wk 4**
- DTG/ABC/3TC PO QD (n = 283)

**Wk 48 Primary Endpoint**
- Comparator arm patients eligible to receive CAB + RPV in extension phase after Wk 52 (ATLAS-2M study)

**Day 0**
- CAB 30 mg + RPV 25 mg PO QD (n = 308)

**Wk 96**
- Continue DTG/ABC/3TC PO QD (n = 283)

**Primary endpoint for both trials:** HIV-1 RNA ≥ 50 copies/mL at Wk 48 by FDA Snapshot in ITT-E

**ART-naive patients with HIV-1 RNA ≥ 10⁷ copies/mL, HBsAg negative, no NNRTI RAMs but K103N permitted (N = 629)**

**Adults on stable ART (either first or second regimen) with HIV-1 RNA < 50 copies/mL for ≥ 6 mos with no previous VF (N = 616)**

Primary Endpoint (HIV-1 RNA ≥ 50 copies/mL) LA CAB + RPV noninferior to continued BL ART

Key Secondary Endpoint (HIV-1 RNA < 50 copies/mL) LA CAB + RPV noninferior to continued BL ART

*Adjusted for sex and BL third agent class.

**What ART to start with?**
Recommended and preferred regimen
International guidelines

*All have INI as preferred 1st option*

<table>
<thead>
<tr>
<th>GUIDELINES</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>INSTI</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>EACS 2018</td>
<td>TAF/FTC</td>
<td>RPV**</td>
<td>DTG</td>
<td>DRV/c or /r</td>
</tr>
<tr>
<td></td>
<td>TDF/FTC</td>
<td></td>
<td>RAL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABC/3TC*</td>
<td></td>
<td>EVG</td>
<td></td>
</tr>
<tr>
<td>DHHS 2019</td>
<td>TAF/FTC</td>
<td>–</td>
<td>DTG</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>TDF/FTC</td>
<td></td>
<td>BIC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABC/3TC*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IAS USA 2018</td>
<td>TAF/FTC</td>
<td>–</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>ABC/3TC*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO 2019</td>
<td>TDF/XTC</td>
<td>–</td>
<td></td>
<td>–</td>
</tr>
</tbody>
</table>

**Recommended in certain clinical situations DHSS 2019**

- 2NRTI+NNRTI  **TDF/FTC/ DOR/** ou EFV ou RPV
- **DTG/3TC**  when NRTI use not optimal
- Boosted PI+2 NRTI: prefer DRV
NAMSAL and ADVANCE: Study Design

- Multicenter, randomized, open-label phase III trials[^1-3]

**NAMSAL: Cameroon**
- ART-naive adults with HIV-1 RNA > 1000 c/mL (N = 613)

**ADVANCE: South Africa**
- ART-naive patients (≥ 12 yrs) with HIV-1 RNA ≥ 500 c/mL (N = 1053)

**Primary Endpoint (Both Trials)**
HIV-1 RNA < 50 c/mL at Wk 48 by FDA Snapshot in ITT population (noninferiority margin: -10%)[^4,5]

# NAMSAL and ADVANCE: Progressive Weight Gain and Clinical Obesity

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NAMSAL</th>
<th>ADVANCE</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Δ in weight, kg</td>
<td>DTG + 3TC/3TC/TDF (n = 293)</td>
<td>EFV + 3TC/3TC/TDF (n = 278)</td>
<td></td>
</tr>
<tr>
<td>Wk 48</td>
<td>+5</td>
<td>+3</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Wk 96</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Mean Δ in BMI at Wk 48</td>
<td>+1.7</td>
<td>+1.2</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Treatment-emergent overweight (BMI 25-29.9), %</td>
<td>16</td>
<td>17</td>
<td>NS</td>
</tr>
<tr>
<td>Wk 48</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Wk 96</td>
<td>NA</td>
<td>NA</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment-emergent obesity (BMI ≥ 30), %</td>
<td>12</td>
<td>5</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Wk 48</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Wk 96</td>
<td>NA</td>
<td>NA</td>
<td>&lt; .01</td>
</tr>
</tbody>
</table>

Hill. IAS 2019. Abstr MOAX0102LB.
Reasons to challenge triple ART
Using non triple drug strategies

Context
- Earlier ART initiation
- Recent / New drugs more potent and robust
- Decades of suppressive ART needed with prolonged drug exposure
- Preserve drug options

Challenges
- Reduce chemical burden
- Maintain long life viral suppression
- Keep ART simple
- Minimize toxicity Adjust to comorbidities
- Avoid drug-drug interactions
- Optimize ART Cost

The Dogma
- Viral load undetectable
  Rather than the number of drugs
- Undetectable = untransmittable

Why more drugs if we can get/maintain viral suppression with less
Towards Drug-reduced Strategies

- Dose reduction
- Dual therapy
- Intermittent therapy

- Adjust ARV to ZERO replication
- Reduce drug burden
- Spare ARV capital
Drug reduced suppressive ART
Dose reduction in context of 3-DR

- Dosage reduction
  Many ARV developed with highest dosage
- Reduce toxicity
  - EFV 400 mg
  OMS guidelines 2019
  Darunavir
  - 600 or 400 mg

3-DR dose reduction

Efavirenz 400 mg
Encore WHO Mexico
Darunavir/r 400/100 mg
Darulight ANRS
WHHRI 052
Darunavir/r 600/100 mg

Important to prevent toxicity; to maintain a class and minimize AE; reduce cost
Reducing drug burden
Dual Therapies (2-DR)

**Initiation**
- **IP / 3TC**
  - LOPI/3TC  GARDEL
  - DRV /3TC  ANDES
- **INI + IP**
  - RAL/DRV  NEAT-01
  - LPV/RAL Progress
- **DTG / 3TC**
  - PADDLE
  - ACTG 5353
  - GEMINI

**Long term**
- **PI / 3TC**
  - LOPI/3TC
  - DRV /3TC
  - ATV/r /3TC
- **INI + NNRTI**
  - RAL/ETR  ETRAL
  - DTG/RPV  SWORD
  - CAB/RPV  LATTE
- **DTG + 3TC**
  - LAMIDOL
  - TANGO
**Dual therapy switch**

**DTG + RPV**  
**SWORD-1 et SWORD-2**

- **2 RCT**
  - DTG/RPV: 511 pts
  - Maintain ARV: 513 pts
- **CD4**: 611 /mm³
- **TAR**
  - TDF: 75% NNRTI:54%
  - IP: 26% INI:20%

**Week 100: 93% efficacy**
Overall 10/990 VF
Low resistance emergence: 3 with NNRTI
RAM


1 seul cas resistance K101K
Sensible RPV
1433 naive patients
- VL: 1000-500 000 cp/ml
- CD4 > 200/mm3

Baseline
Med VL : 4.45 log HIV RNA
% > 100 000 : 20%
CD4 : 427/mm3

End point : % VS at W48
Follow up : continuation phase for DTG/3TC group
GEMINI  Dual Therapy in naive patients

**DTG/3TC vs DTG/TDF/FTC**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Responders, n (%)</th>
<th>Adjusted difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG + 3TC</td>
<td>616/716 (86.0)</td>
<td>−3.4 (−6.7, 0.0)</td>
</tr>
<tr>
<td>DTG + TDF/FTC</td>
<td>642/717 (89.5)</td>
<td></td>
</tr>
</tbody>
</table>

Non-inferiority criteria were met for GEMINI-1, GEMINI-2, and the pooled analysis

Cahn et al.  Lancet  IAS 2019; Mexico City, Mexico. Slides WEAB0404L
DTG + 3TC Noninferior to DTG + TDF/FTC in Treatment-Naive Patients at Wk 48

DTG + 3TC was noninferior vs 3-drug therapy, no resistance in either arm

- 6 Confirmed VF with DTG + 3TC:
- 4 Confirmed VF with DTG + TDF/FTC
- No treatment-emergent INSTI or NRTI mutations in patients with VF in either arm
- Bone and kidney safety markers more favorable with DTG + 3TC vs DTG + TDF/FTC

*Adjusted for HIV-1 RNA (≤ vs > 100,000 copies/mL), CD4+ cell count (≤ vs > 200 cells/mm³), and study (GEMINI-1 vs GEMINI-2). †ITT-E: -1.7% (95% CI: -4.4% to 1.1%) PP†: -1.3% (95% CI: -3.9% to 1.2%)
TANGO DTG/3TC Switch study

DTG/3TC is non inferior to TAF-based regimen at Week 48

0/352 participants in the DTG/3TC group and 2/358 participants in the TAF-based regimen group had HIV-1 RNA ≥50 c/mL at Week 48

No resistance
MOBIDIP Study: switch to PI/r + 3TC vs PI/r mono

- **Design**
  - Randomisation: 1:1 Open-label
  - Eligibility criteria:
    - ≥18 years
    - HIV RNA < 200 c/mL > 6 months on 2LADY study (2nd line study)
      - on LPV/r + TDF + FTC
      - or LPV/r + ABC + ddI
      - or DRV/r + TDF + FTC
    - Stable cART in past 3 months
    - No prior virological failure
    - CD4 > 100/mm$^3$
    - Adherence ≥ 90%
    - HBs Ag negative
  - MOBIDIP Study: switch to PI/r + 3TC vs PI/r mono
    - LPV/r monotherapy (n = 82)
      - LPV/r + TDF + FTC (N = 152)
    - DRV/r monotherapy (n = 50)
      - DRV/r + 3TC 300 mg QD (n= 50)

- **Objective**
  - Primary Endpoint: failure rate at W96 by ITT, defined as 1) a confirmed HIV RNA > 500 c/mL, 2) reintroduction of the NRTI backbone or 3) interruption of the PI
  - March 2016: Monotherapy arm discontinued following DSMB meeting

*Ciaffi L, Lancet HIV 2017, May 28, 2017 (Epub ahead of print)*
## MOBIDIP: Switch to PI/r + 3TC vs PI/r mono

<table>
<thead>
<tr>
<th></th>
<th>PI/r monotherapy</th>
<th>PI/r + 3TC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 133</td>
<td>N = 132</td>
</tr>
<tr>
<td>HIV RNA &lt; 50 c/mL, %</td>
<td>80</td>
<td>83</td>
</tr>
<tr>
<td>CD4/mm³, median</td>
<td>498</td>
<td>472</td>
</tr>
<tr>
<td><strong>Nadir CD4 &lt; 100/mm³, %</strong></td>
<td>56</td>
<td>52</td>
</tr>
<tr>
<td>PI/r = DRV, %</td>
<td>42</td>
<td>33</td>
</tr>
<tr>
<td><strong>Months on first-line cART, median</strong></td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td><strong>Months on second-line cART, median</strong></td>
<td>37</td>
<td>38</td>
</tr>
<tr>
<td>M184V at first failure, %</td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td>Resistance to one 2nd line-drug, %</td>
<td>61</td>
<td>60</td>
</tr>
<tr>
<td>Resistance to two 2nd line-drug, %</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td><strong>Failure, ITT, % (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virological failure, N</td>
<td>24.8 (17.7 – 33.0)</td>
<td>3.0 (0.8-7.6) (p &lt; 0.001)</td>
</tr>
<tr>
<td>NRTI reintroduction, N</td>
<td><strong>28</strong> *</td>
<td><strong>3</strong> *</td>
</tr>
<tr>
<td>Death, lost to follow-up, N</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

* All failure resuppressed to HIV RNA < 200 c/mL a median of 10 weeks after NRTI reintroduction

Intermittent 3-DR regimen

**BREATHER** Etude rando.pilote
199 enfants /ados  TAR: 2NRT/EFV
TAR 5 JOURS /7

**Etude 4D ANRS 162**
Etude pilote 100 patients contrôlés
TAR 4 JOURS /7

Succès 96% ; 3 échecs ; pas de Résistance

ART Intermittent

**A**

- Short cycle therapy
- Continuous treatment

- Number at risk
  - Short cycle therapy: 99, 99, 98, 98, 96, 92, 90
  - Continuous therapy: 100, 100, 99, 98, 95, 88, 87

- Probability of viral rebound (%)
  - Weeks from randomisation: 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56

**B**

- Primary analysis
- Unadjusted analysis
- Crude proportion difference
- Per-protocol analysis

- Non-inferiority margin
  - -0.12 to 0.16

- Probabilities

- Time (weeks): 100, 99, 98, 96, 96, 96, 95

Results in 2019
QUATUOR
A switch study to 4 days a week regimen

Screening Phase
- VL < 50 c/mL for ≥12 months
- No genotype resistance
- CD4 > 250 cells/mm$^3$
- PI-, NNRTI- or INI-based regimen with a 2 NRTI

Controlled Phase
- 4 D/7
  n = 320
- 7 D/7
  n = 320

Long-term Follow-up
- 4 D/7

Baseline characteristics
- 640 Patients; 5 years VS; CD4: 690 /mm$^3$
- INI: 48%  INNTI: 47%
QUATUOR
A switch study to 4 days a week regimen

Virological failure

<table>
<thead>
<tr>
<th>ITT - KM</th>
<th>PP - KM</th>
</tr>
</thead>
<tbody>
<tr>
<td>+0.6</td>
<td>+0.6</td>
</tr>
</tbody>
</table>

Difference (95% CI) of proportion

FDA Non-inferiority margin

<table>
<thead>
<tr>
<th>VF</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm INI</td>
<td>3</td>
</tr>
<tr>
<td>Arm INNTI RAM</td>
<td>3</td>
</tr>
<tr>
<td>Arm INNTI</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (DTG)</td>
</tr>
<tr>
<td>3 (RPV)</td>
</tr>
<tr>
<td>1 (K101E/K)</td>
</tr>
</tbody>
</table>

Treatment differences adjusted by third agent stratification using the Cochran-Mantel-Haenszel method
HIV drug pipeline under clinical evaluation

**Attachment**

- CD4
- Chemokine co-receptor

**Fusion**

- VRC01
- VRC01-LS

**Entry inhibitors**

- Fostemsavir (GSK-934; FTR)
- Cenicriviroc (TBR-652; CVC)
- Sifuvirtide (FS-0101)
- Albuvirtide (FB006M; ABT)

**Monoclonal antibodies (mAb)**

- UB-421 (CD4 receptor)
- PRO-140 (CCR5 receptor)
- Ibalizumab (TMB-355)
- VRC01

**NRTIs/NtRTIs ('nukes')**

- Islatravir (MK-8591)
- GS-9131

**NNRTIs ('non-nukes')**

- Elsulfavirine (VM1500)
- Dapivirine (TMC120; DPV)
- PC-1005 (MIV-150/zinc acetate)

**Integrate inhibitors**

- Cabotegravir-LAI (GSK-744; CAB)
- MK-2048

**Integrase inhibitors**

- GS-PI1
- GS-CA1

**Protease inhibitors**

- Rilpivirine-LAI (TMC278; RPV)
- Dapivirine (TMC120; DPV)

**Capsid inhibitors**

- Dapivirine (TMC278; RPV)

**Translation**

**Assembly/cleavage**

**Maturation inhibitors**

- GSK2838232
- MK-8507
- ABX464

**Unique/unknown MoA**

- LEDGINs

**HIV LIFE CYCLE**

1. Attachment
   - CD4
   - Chemokine co-receptor
2. Fusion
   - VRC01
   - VRC01-LS
3. Reverse transcription
4. Integration
5. Transcription
6. Translation
7. Assembly/cleavage
8. Maturation
ART reduced regimen in real life
Experience of Pitié Salpétrieire

suppressive ART in 2017/2018
3480 patients with VL<50 cp/mL

<table>
<thead>
<tr>
<th>ART</th>
<th>2017 n %</th>
<th>2018 n %</th>
</tr>
</thead>
<tbody>
<tr>
<td>n= 2941 pts</td>
<td>n= 3480 pts</td>
<td></td>
</tr>
<tr>
<td>Triple therapy</td>
<td>2026, 69%</td>
<td>2407, 69,2%</td>
</tr>
<tr>
<td>7 days /7</td>
<td>1938, 66%</td>
<td>2187, 62,8%</td>
</tr>
<tr>
<td>Intermittent</td>
<td>88, 3%</td>
<td>220, 6,4%</td>
</tr>
<tr>
<td>4 days /w</td>
<td>72, 2,4%</td>
<td>137, 3,9%</td>
</tr>
</tbody>
</table>

Drug reduced regimen
33% in 2017
36% in 2018
The future of ART

- Viral suppression is the **only dogma** in ART management
- Viral load / resistance test cannot be separated from drugs
- Empower patients in their follow up
- ART is the way to stop HIV/AIDS if all HIV+ are tested and suppressed
- ARV drugs prophylaxis is of major importance in key populations

- **Decreasing ART exposure**
  - Decreasing drug dose
  - Decreasing numbers of drugs*

- **Long acting drugs**
  - Long-acting oral agents (QW)
  - Implantable agents
  - Long-acting injectables*

- **Immune based therapies**
  BnAB : neutralizing AB