HIV Therapy: what is the magic number?

The Virologist’s perspective

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AG Marcelin has no commercial interests.

AG Marcelin has received travel grants, honoraria, and study grants from various pharmaceutical companies including Bristol-Myers-Squibb, Gilead Sciences, Merck-Sharp & Dohme-Chibret, Roche and ViiV Healthcare.

AG Marcelin prepared the content of this presentation using his own material with no commercial input.

AG Marcelin may discuss cases and circumstance when drugs are used off label; this is his own personal clinical experience. For the proper use of medications, please review the Product Monographs.
Current recommendations

• HIV infection is deleterious starting in the very first days following infection
• No current strategy for HIV cure
• HIV has to be controlled with life long ART
• 3-drugs combination is still recommended for all patients starting treatment
• Recent guidelines provide some recommendations for simplification in virologically suppressed patients
1987
AZT monotherapy

1994-1995
NRTI dual therapy

1996-1997
2 NRTI + PI

Multiple Mutations in HIV-1 Reverse Transcriptase Confer High-Level Resistance to Zidovudine (AZT)

B.A Larder et al; Science 1989

Quantitative detection of HIV-1 drug resistance mutations by automated DNA sequencing

B.A Larder et al; Nature 1993
HIV Population Dynamics in Vivo: Implications for Genetic Variation, Pathogenesis, and Therapy

John M. Coffin

• Prob. 1 virus resistant to drug A 1/10 000 to 100 000 ($10^4$ to $10^5$)
• Prob. 1 virus resistant to drug B 1/10 000 to 100 000 ($10^4$ to $10^5$)
  • **Prob. 1 virus resistant to drugs A+B** $10^4$ /$10^5$ x $10^4$ /$10^5$ = $10^8$ to $10^{10}$
• Prob. 1 virus resistant to drug C 1/10 000 to 100 000 ($10^4$ to $10^5$)

**Probability 1 virus resistant to drugs A + B + C = 1/$10^{12}$ to $10^{15}$**

<<< $10^9$ of new viruses/day
Do we still need 3 ARV to achieve viral suppression?

• Patients are initiated at much earlier stages (2010-2013): shift in
  • CD4: 200 to 405 cells/mm$^3$
  • HIV VL: 5 to 4.58 log$_{10}$ cps/ml

• Need for evaluation of “lighter” antiretroviral regimens, i.e. dual or single ARV combinations with potential benefits
  • reduced toxicity
  • better tolerability
  • less resistance
  • class-sparing
  • lower costs

Rather than triple therapy for all, the new dogma should become ART and lifelong viral suppression for all
Ideal candidates

• High antiviral potency
• High robustness in term of genetic barrier to resistance
• Favorable pharmacokinetics properties (minimal inter and intra variability)
these immature virions produced in the presence of PIs are incapable of efficiently completing entry (1), reverse transcription (2), and post–reverse transcription steps (3).

At clinical concentrations, the entry inhibition by PIs is a major component of their overall inhibitory potential... PIs act like multiple drugs in one.
Virologic robustness of DTG

- Long **dissociative half life** from integrase (71h)
- High **inhibitory quotient** (x19)
- High **virologic potency** (-2,46 log in monotherapy)
- No **resistance mutations** (INTI and INSTI) in any randomised clinical trials in naive or suppressed patients

Naïve patients

• 1 Drug Regimen: PI based
  – LPV/r (MONARK): inferior efficacy vs LPV/r + AZT/3TC, emergence of resistance in 3/21 in monotherapy (L76V, M46I)
    • DEFINITELY NOT RECOMMENDED

• 2 Drugs Regimen: PI based

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• RAL and MVC can not be substitute to 2 NRTIs
NEAT 001: emergence of resistance

Table 2. Resistance mutations in the raltegravir plus darunavir/ritonavir arm

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No RAM at virological failure in the standard TDF/FTC/DRVr regimen

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Naïve patients

- 2 DR regimen (3TC + DTG)
  - PADDLE: pilot study in 20 patients with VL < 100 000 cp/ml
    - Rapid virologic suppression
  
  - GEMINI: phase 3 study evaluating 3TC + DTG vs TDF/FTC + DTG (ongoing)

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Cahn P, IAC 2016, Abs. FRAB0104LB
Virologically suppressed patients

- 1 DR

  - Boosted PI monotherapy:
PI/r monotherapy is possible if...

• Clinical criteria
  • High adherence
  • No previous CNS disorders
  • Nadir CD4 > 200/mm3

• Virological
  • Previous long term virologic suppression
  • Low residual viremia (< 1 copy/ml)
  • Low viral DNA before switch
  • No previous failure or resistance
  • No HBV chronic infection
FHDH-ANRS CO4 cohort: PI/r mono (2006-2010, 529 patients)

Duration of undetectable viremia since last rebound

- < 12 months: \( n = 88 \)
- 12-23 months: \( n = 85 \)
- ≥ 24 months: \( n = 356 \)

Virological failure at 12 months (95% CI)

- 38% (27-52)
- 26% (17-39)
- 15% (12-20)

M. Guiguet et al; AIDS 2012
**Ultrasensitive viral load**

**Plasma HIV-1 RNA Levels During Antiretroviral Therapy:**

**How Low Is Low Enough?**

**Factors Associated With Virological Failure in HIV-1–Infected Patients Receiving Darunavir/Ritonavir Monotherapy**

Baseline ultrasensitive VL <1 copy/mL was independently associated with a decreased risk of VF.

*S.Lambert-Niclot et al; JID 2011*

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**Very Low Level Viremia**

**Single Copy Assay**

**RNA not detected (No signal)**
Levels of HIV-DNA in patients with suppressive antiretroviral therapy

A cross-sectional, multicentre study of patients receiving ART for more than 3 years, HIV-RNA less than 50 copies/ml for more than 2 years and CD4+ cell count more than 350 cells/ml.

Median HIV-DNA was 323 copies/10^6 PBMCs

<table>
<thead>
<tr>
<th>Range</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
<td>28.3%</td>
</tr>
<tr>
<td>150-1000</td>
<td>55.4%</td>
</tr>
<tr>
<td>&gt; 1000</td>
<td>16.3%</td>
</tr>
</tbody>
</table>

=> French guidelines for PI/r: HIV DNA < 200 copies/10^6 PBMCs and not > 1000 copies/10^6 PBMCs.

L. Cuzin et al; AIDS 2015
In this real-life setting, genotyping on PBMC does provide information with good PPV when compared to past RNA sequencing. However, negative results from PBMC must be interpreted with caution.

=> PI/r: no previous failure or resistance
Virologically suppressed patients

• 1 DR
  – DTG monotherapy: **NOT RECOMMENDED**
    • **DOMONO: Switch to DTG Monotherapy in Virologically Suppressed Pts Not Sufficient**
      ▪ Randomized comparison of switch to DTG 50 mg QD monotherapy vs continued baseline ART for 24 wks in virologically suppressed pts with no previous VF
      ▪ At Wk 24, DTG monotherapy non inferior to continued baseline ART for maintained HIV-1 RNA < 200 c/mL
      ▪ Study d/c early because of high VF rate after 48 wks of DTG monotherapy
        – VF in 8/77 pts with DTG monotherapy vs 3/152 pts on combination ART in concurrent control group ($P = .03$)
        – Among 6 VF cases with resistance data in DTG monotherapy group, 3 developed INSTI resistance

Virologically suppressed patients

- 2 DR
  - PI/r based + 3TC
    - DUAL-GESIDA 8014: DRV/r + 3TC Dual ART was non inferior to triple ART (TDF/FTC or ABC/3TC + DRV/r) at Wk 48
      » No resistance mutations in the 2 dual-therapy patients who experienced virologic failure

- ANRS 12286/MOBIDIP: after viral suppression with boosted protease inhibitor plus NRTI in second-line ART, maintenance therapy with boosted PI plus 3TC was associated with a higher rate of success than PI monotherapy, despite the presence of M184V (96%) at first-line treatment failure

M184V: reduced replicative capacity

=> residual activiral effect of 3TC which prevent relapse of viral replication in combination with PI/r in patients already suppressed
Virologically suppressed patients

• 2 DR
  – INSTI based
    • NNRTI
      – ANRS 163 ETRAL: non comparative, open-label, single-arm multicenter trial evaluating RAL + ETR
      – SWORD: switch from suppressive ART to DTG + RPV was non inferior to continued baseline ART at Wk 48 (1 pt with confirmed criteria for virologic withdrawal at Wk 36 in DTG + RPV arm had K101K/E, no INSTI resistance)

• 3TC
  – LAMIDOL: switch to DTG + 3TC was effective in maintaining viral suppression at Wk 48 (no INSTI resistance in 3 pts with virologic failure)
Conclusions

• Triple therapy: remains the gold standard for virologists (potency, no resistance)

• HIV treatment is currently evolving towards individualized therapy
  • To adjust chronic therapies to each individual
    • Ex: 20% of patients are receiving dual therapies in our clinical center

• We need to evaluate these strategies and to develop new tools
Conclusions

• Monotherapy
  • Not recommended in naïve patients
    • Lack of virological potency
    • Risk of emergence of resistance (not acceptable after first line failure)

• Possible in suppressed patients
  • With PI/r
    • Despite LLV, no emergence of resistance
    • Clinical and virological tools to identify good candidates (UsVL < 1 cp/ml, HIV DNA < 2.3 log and no resistance)
    • Represents only 4% of patients in our clinical center...
Conclusions

• **Dual therapy**
  • In naïve:
    • MVC or RAL cannot be substitute to 2 NRTIs
      • Even if antiviral potency independently, lack of efficacy in combination
      • Emergence of resistance (DRV does not protect from selection of integrase resistance)
      • Waiting for large clinical trials results with 3TC + DTG
  
  • In suppressed:
    • Several options: with PI/r or DTG
    • RT inhibitors are still needed: 3TC or NNRTI (RPV, ETR)
    • 3TC can be substitute to 2 NRTIs even when it shouldn’t work...

• Be careful with HBV!!!!
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