Clinical Implications of Low level viremia / failure and resistance

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Cattedra di Virologia

Santiago, 30th June 2017
Today, thanks to the modern potent regimens, more than 90% of patients starting a first-line regimen achieve virological suppression.

Almost every step of HIV replication is target of at least one drug.

1. Entry inhibitor: MVC
2. Fusion inhibitor (FIs): T20
3. Integrase inhibitors (INIs): RAL, EVG, DTG
4. Protease inhibitors (PIs): SQV, IDV, RTV, NFV, fAPV, LPV, ATV, TPV, DRV


9 Nucleoside reverse transcriptase inhibitors (NRTIs):
AZT, ddI, ddC, d4T, 3TC, ABC, TDF, FTC, TAF

5 Non-nucleoside reverse transcriptase inhibitors (NNRTIs):
EFV, NVP, DLV, ETR, RPV

Indeed…
Proportion of patients with a VL<=80 copies/mL at 12 months from starting their first ART regimen by calendar year of initiation

……..15188 Icona patients.....
Definitions of Virological Failure

The inability to achieve or maintain suppression of viral replication to an HIV RNA level <200 copies/mL. **DHHS adult & adolescent guidelines, 2016.**

Confirmed HIV-VL > 50 copies/mL 6 months after starting therapy (initiation or modification) in persons that remain on ART. Depending on the HIV-VL assay, this limit could be higher or lower. **European Guidelines, 2016.**

Indica il mancato raggiungimento entro 24 settimane, o la perdita, della soppressione virologica dopo l’inizio di una cART (2 valori consecutivi di viremia > 50 copie/mL). **Italian Guidelines, 2016.**

The inability to achieve or maintain viral suppression below a certain threshold. **Viral failure is defined by a persistently detectable viral load exceeding 1000 copies/mL** (two consecutive viral load measurements within a 3-month interval with adherence support between measurements) **after at least 6 months of using ART. WHO guidelines, 2016.**
In the long-term management of HIV infection, the stable maintenance of undetectable HIV over the years is more important than the mere success of the first regimen.
Factors influencing long-term viral suppression

\[ \text{Durability} = \text{Adherence} + \text{Drug Levels} + \text{Genetic Barrier} - \text{Baseline Mutations} - \text{Baseline Burden} \]

- **Patient**: Adherence
  - Convenience & tolerability
- **Drug**: Drug Levels
  - Height and duration of drug exposure
  - Adverse effects
- **Virus**: Genetic Barrier
  - Number and type of mutations required for resistance development
  - Number and type of mutations present at baseline
    - Subtype
  - Baseline Burden

Svicher et al submitted
Therapy insights today

• Treatment is life-long (or at least for decades)
• Therapy is successful only if maintained for decades, not for months or a few years
• Switch to new ARTs is a natural event in the course of long-term therapies (failure, toxicity, intolerance etc)
• Preservation of future therapeutic options is mandatory in this context
• Avoiding the emergence of resistance / cross resistance is, in this frame, one of the major factors to be considered
  – Otherwise, a clinical price will be paid, although later than in the past…..
Therefore………..

- Our endeavour today has switched from treating the resistant virus to preventing its emergence and consolidation
  - Although resistant viruses are still an issue in a number of patients

- Long-term success will require major attention in this matter

Virological rebound is still a concern
Overall, by 96 weeks after achieving virological success, the probability of virological rebound was 17.5%.

Patients (N=1,671) followed after achieving VS regardless therapy changes or interruptions. Virological rebound defined as the first of 2 consecutive viremia values >50 copies/mL after achieving VS. VS: virological success.
By 96 weeks after achieving virological success, patients having pre-HAART viremia >500,000 copies/mL showed the highest probability of experiencing virological rebound compared to other pre-HAART viremia ranges.

Pre-HAART viremia ranges (copies/mL):
- <30K
- 30-100K
- 100-300K
- 300-500K
- >500K

Rebound as the first of 2 consecutive HIV-RNA >50 copies/mL: 17.5%

Rebound as the first of 2 consecutive HIV-RNA >200 copies/mL: 12%

Patients (N=1,671) followed after achieving VS regardless therapy changes or interruptions. Virological rebound defined as the first of 2 consecutive viremia values >50 copies/mL after achieving VS. <30K: <30,000. 30-100K: 30,000-100,000. 100-300K: 100,000-300,000. 300-500K: 300,000-500,000. >500K: >500,000. HAART: highly active antiretroviral therapy. VS: virological success.
The majority of virological rebounds show low level viremia that represents one of the most frequent reasons of uncertainty in clinical decisions.

Indeed........
LLV & Time to next visit

Pts with optimal suppression

Pts with low level viremia/blips

Viremia and viral blips generate uncertainty among clinicians and patients

Presented at the 10th Eu Meeting on HIV & Hepatitis, 28-30 March 2012, Barcelona
# Definitions of virological failure

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Low level viremia</td>
<td>HIV-1 plasma viral load of 50-500 cpm.(^1)</td>
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<tr>
<td>Viral blip</td>
<td>An episode of low level viremia that is preceded and followed by suppression below the quantification limit of the assay.</td>
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<tr>
<td>Persistent low level viremia</td>
<td>At least two consecutive episodes of low level viremia.</td>
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<tr>
<td>Very low level viremia</td>
<td>HIV-1 plasma viral load of &lt;50 cpm detected by clinical assays with quantification cut-offs lower than 50 cpm.</td>
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<tr>
<td>Residual viremia</td>
<td>Cryptic viremia during cART that is often 1-10 cpm and unaffected by treatment intensification (6-13).</td>
</tr>
<tr>
<td>Virological failure</td>
<td>HIV-1 plasma viral load of &gt;1000 cpm after previously attaining a plasma viral load of &lt;1000 cpm.(^2)</td>
</tr>
<tr>
<td>Low level viral rebound</td>
<td>At least one HIV plasma viral load of 50-500 cpm in a patient who previously attained viral suppression to &lt;50 cpm.</td>
</tr>
<tr>
<td>High level viral rebound</td>
<td>At least one HIV plasma viral load of 500-1000 cpm in a patient who previously attained viral suppression to &lt;50 cpm.</td>
</tr>
<tr>
<td>Viral rebound with HIV resistance</td>
<td>The development of new HIV drug resistance mutations in the context of at least one HIV plasma viral load &gt;50 cpm.</td>
</tr>
</tbody>
</table>

\(^1\)Some authors have defined low level viremia with an upper plasma viral load of 1000 cpm.

\(^2\)There is significant heterogeneity in the definition of virological failure across guidelines (Table 5).

Abbreviations: cpm: copies per milliliter;
Viral blip

Ryscavage P et al., AAC2014
Low level viremia (LLV) and very low level viremia (VLLV)

Ryscavage P et al., AAC2014
Residual viremia (<10 copies/ml) can persist despite long term virological success

Using a single-copy HIV-1 RNA assay, >80% of individuals had stable HIV-1 viremia after 60 weeks of cART, with a median pVL of 3.1 copies/ml (range, 1 to 49 copies/ml).

HIV-1 RNA Levels Over 50 wk of Suppressive Antiretroviral Therapy
Residual Viraemia

- Ongoing virus replication in sanctuary cellular or body compartments due to poor drug penetration or activity

Two models to explain residual viraemia

- Virus reactivation in latently infected cells in response to stochastic antigenic stimulation, with presence of HAART ensuring that new cells cannot be productively infected

It is possible that both mechanisms contribute to residual viremia
Transient low level viremias, with plasma HIV-1 RNA levels in the range of 50 to 400 copies/ml, have been reported to occur in 25 to 40% of adults in whom viral replication appeared to have been suppressed by HAART.


Very low-level viremia (<50 copies/ml) is associated with virological failure

Plasma HIV-1 RNA detection below 50 copies/ml and risk of virologic rebound in patients receiving highly active antiretroviral therapy

Time to virologic rebound according to the T0 viral load

VR: single VL>50 copies/mL

VR: confirmed or last available viral load >50 copies/mL

Very low-level viremia (<50 copies/ml) is associated with virological failure

Ultrasensitive assessment of residual low-level HIV viremia in HAART-treated patients and risk of virological failure

Risk of virologic failure (confirmed viral load > 50 copies/ml) in the following 4 months for patients with an HIV-RNA < 3 copies/ml was 0.4% compared with a 3.2% risk for those with any value of low-level viremia (P < 0.0001; odds ratio 7.52, 95% CI from 3.8 to 15.0).

Linear relationship between the HIV-RNA level and risk of virological failure
FIGURE 1. Rates of viral load rebound above 50 copies/ml and above 400 copies/ml over 12 months according to the viral load (VL) level detected at an arbitrary time point during suppressive antiretroviral therapy (referred to as time zero, T0). The risk of viral load rebound was significantly higher in patients that at T0 showed either detectable HIV-1 RNA between 40 and 49 copies/ml (40–49 cps/ml) or qualitative HIV-1 RNA detection below 40 copies/ml (RNA+), relative to patients with undetectable HIV-1 RNA (RNA−) [13**].

Doyle and Geretti, Curr Opin Infect Dis 2012
Very low-level viremia (<50 copies/ml) is associated with virological failure

HIV DNA loads, plasma residual viraemia and risk of virological rebound in heavily treated, virologically suppressed HIV-infected patients

Residual viraemia (<50 copies/ml) was independently associated with virological rebound

RV was defined by any HIV RNA values detectable below 50 copies/mL.

Gianotti et al., CMI 2014
Impact of low-level viraemia on virological failure in HIV-1-infected patients with stable antiretroviral treatment

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ABSTRACT:

Background: Low level viraemia (LLV) occurs in 20-40% of patients achieving viral suppression with antiretroviral therapy (ART). The risk of virological failure (VF: confirmed HIV-RNA >200 copies/mL) in these patients is still a matter of debate.

Methods: Prospective cohort study in HIV-infected adults attending the HIV clinic of a tertiary-care hospital in Spain. Patients with HIV-RNA <25 copies/mL and stable ART for at least 6 months presenting LLV (defined as a HIV RNA between 25-1000 copies/mL) from January/2011 to January/2013 were included and followed until VF or end of follow-up in June 2014.

Results: Three-hundred out of 1733 (17.3%) patients with undetectable viraemia for 4.2 years, showed LLV: 25-50 copies/mL in 167 (55.7%) patients; 51-200 copies/mL in 111 (37%) and 201-1000 copies/mL in 22 (7.3%) cases. After a median follow-up of 2.6 years, 23 (7.7%) patients presented VF. No patient with a single or multiple unconfirmed LLV went on to develop to VF. HIV-RNA >200 copies/mL (HR 59.6; 95%CI 15.7-227), PI/r-based dual therapy (HR 10.2; 95%CI 2.1-49.9), PI/r monotherapy (HR 7.9; 95%CI 1.4-43.3) were associated with VF. Persistent LLV, defined as HIV-RNA <200 copies/mL in at least 3 consecutive samples, for at least 12 weeks, was detected in 27 (1.6%) patients and 14 (51.9%) of them evolved to VF.

Conclusions: Nearly a fifth of patients on suppressive-ART showed LLV and 8% of them developed VF. HIV-RNA >200 copies/mL was the strongest predictor of VF. Over half of patients with persistent viraemia <200 copies/mL showed VF.

Accepted 18 December 2015, published online 12 January 2016

Running head: Low-level viraemia and virological failure

Navarro et al. Antivir ther, 2016
HIV-RNA > 200 copies/ml, PI/r-based dual therapy and PI/r monotherapy were associated with virological failure.
What about viral blips?

Is their magnitude associated with virological failure?
Very low level viraemia and risk of virological failure in treated HIV-1-infected patients


Objectives
The aim of the study was to investigate whether very low level viraemia (VLLV) [20–50 HIV-1 RNA copies/ml] was associated with increased risk of virological failure (VF) as compared with persistent full suppression (< 20 copies/ml).

Methods
From the VACH Cohort database, we selected those patients who started antiretroviral therapy (ART) after January 1997 and who achieved effective viral suppression [two consecutive viral loads (VLs) < 50 copies/mL] followed by full suppression (at least one VL <20 copies/mL). We carried out survival analyses to investigate whether the occurrence of VLLV rather than maintaining full suppression at < 20 copies/mL was associated with virological failure (two consecutive VLs > 200 copies/mL or one VL > 200 copies/mL followed by a change of ART regimen, administrative censoring or loss to follow-up), adjusted for nadir CD4 cell count, sex, age, ethnicity, transmission group, type of ART and time on effective suppression at < 50 copies/mL.

Results
Of 21480 patients who started ART, 13674 (63.7%) achieved effective suppression at < 50 copies/mL, of whom 4289 (31.4%) further achieved full suppression at < 20 copies/mL after May 2009. A total of 2623 patients (61.1%) remained fully suppressed thereafter, while 1666 had one or more episodes of VL detection > 20 copies/mL (excluding virological failure). A total of 824 patients had VLLV after suppression at < 20 copies/mL. VLLV was not associated with virological failure as compared with persistent full suppression [hazard ratio (HR) 0.67; 95% confidence interval (CI) 0.44–1.00], independently of the number of blips recorded (from one to 18).

Conclusions
In our population of HIV-infected patients on ART who achieved viral suppression at < 20 copies/mL, the risk of virological failure was no different for patients who remained fully suppressed compared with those who experienced subsequent episodes of VLLV.
Among patients who achieved full suppression at <20 copies/mL, subsequent VLLV/LLV was not associated with virological failure as compared with persistent full suppression, independently of the number of blips recorded (from one to 18).

Virological failure: 2 consecutive VLs >200 copies/ml or one >200 copies/ml followed by a change of ART.

Kaplan–Meier curves of time free of virological failure for patients with persistent virological suppression and (a) very low level viraemia (VLLV; 20–49 copies/mL), (b) low-level viraemia (50–199 copies/mL) and (c) high-level blips (≥ 200 copies/mL).

Teira et al., HIV Medicine 2016
The incidence of virological failure was significantly higher in patients with transient viremic episodes > 200 copies/mL than in persistently suppressed patients.

Virological failure: 2 consecutive VLs >200 copies/ml or one >200 copies/ml followed by a change of ART.

Kaplan–Meier curves of time free of virological failure for patients with persistent virological suppression and (a) very low level viraemia (VLLV; 20–49 copies/mL), (b) low-level viraemia (50–199 copies/mL) and (c) high-level blips (≥200 copies/mL).

Teira et al., HIV Medicine 2016
When genotypic resistance test should be performed?
Low level viremias have been associated with selection of drug-resistant virus in several (but not all) studies

Cohen Stuart, et al. Transient relapses ("blips") of plasma HIV RNA levels during HAART are associated with drug resistance. JAIDS 2001


Nettles, et al. Intermittent HIV-1 viremia (blips) and drug resistance in patients receiving HAART. JAMA 2005

Sklar, et al. Prevalence and clinical correlates of HIV viremia (‘blips’) in patients with previous suppression below the limits of quantification. AIDS 2002


Santoro MM et al. Reliability and Clinical Relevance of the HIV-1 Drug-Resistance Test in Patients with Low Viremia Levels. CID 2014


Vancoillie L et al. Drug resistance is rarely the cause or consequence of long-term persistent low-level viraemia in HIV-1-infected patients on ART. Antivir Ther 2015
When genotypic resistance test should be performed?

- In acute HIV infection
- In ART-naive patients with chronic HIV infection
- In patients with virologic failure

Drug-resistance testing is **recommended** in patients on combination ART with **HIV RNA levels >1,000 copies/mL** (AI). In patients with HIV RNA levels >500 copies/mL but <1,000 copies/mL, **Testing may not be successful** but should still be considered.

DHHS adult & adolescent guidelines, 2016
When genotypic resistance test should be performed?

- In acute HIV infection
- In ART-naive patients with chronic HIV infection
- In patients with virologic failure

Perform resistance testing on failing therapy (usually routinely available for HIV-VL levels $>350-500$ copies/mL and in specialised laboratories for lower levels of viraemia) and obtain historical resistance testing for archived mutations.
When genotypic resistance test should be performed?

- In acute HIV infection
- In ART-naive patients with chronic HIV infection
- In patients with virologic failure

<table>
<thead>
<tr>
<th>IMPIEGO</th>
<th>RACCOMANDAZIONE (FORZA/EVIDENZA)</th>
<th>RAZIONALE</th>
<th>RIFERIMENTI BIBLIOGRAFICI</th>
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<tbody>
<tr>
<td>Per pazienti in fallimento con viremia &gt; 200 copie/mL al fine di impostare al meglio la cART successiva.</td>
<td>[AI]</td>
<td>E' essenziale che il test venga eseguito mentre la terapia fallita è ancora in corso, al fine di evitare il rischio di falsi negativi.</td>
<td>[19,29]</td>
</tr>
<tr>
<td>Per pazienti in fallimento con viremia 50-200 copie/mL il test è ugualmente consigliato per una corretta impostazione della cART successiva.</td>
<td>[AI]</td>
<td>In pazienti che falliscono una cART con viremia 50-200 copie/mL il test fornisce risultati affidabili e riproducibili, informativi della resistenza emergente a bassi livelli di viremia e predittivi di ulteriore rialzo della viremia. L'efficienza di amplificazione e interpretazione è già circa del 70% con viremia intorno alle 50-200 copie/mL, mentre è &gt; 90% con viremie 500-1000 copie/mL.</td>
<td>[19,34-36]</td>
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An increased number of GRTs have been requested over the years for patients failing with low viremia values.

8,342 genotypic requests from plasma samples of treatment experienced patients stratified by viremia and years. * Update to October 2013.

Santoro et al., update from CID 2014
GRT at low level viremia is reliable and resistance is detectable at all viremia levels!
Overall, the PR/RT genotyping success rate was 96%. Genotyping success was ≥88% above 200 HIV copies/mL. A reasonable chance of success was obtained also between 50 and 200 copies/mL.
A considerable resistance is observed also at low levels of viremia.

Prevalence of samples with at least one major resistance mutation in patients failing PIs (boosted or unboosted), NRTIs or NNRTIs, stratified by viremia.

**P <0.001 (Chi-squared test for trend)**

Prevalence of samples with at least one major resistance mutation in patients failing PIs (boosted or unboosted), NRTIs or NNRTIs, stratified by viremia.
The distribution of drug-resistance stratified for viral load is confirmed also considering samples only from patients failing their first-line regimen.

Prevalence of samples with at least one major resistance mutation in patients failing PIs (boosted or unboosted), NRTIs or NNRTIs, stratified by viremia.

Santoro et al., Poster P-L5 CROI 2014
Raltegravir resistance observed also at low levels of viremia

10.5% (6/57) of isolates from patients with viral load between 51 and 200 copies/mL showed resistance mutations at raltegravir failure, whereas above 200 copies/mL, about 50% of isolates showed the presence of resistance mutations at positions 148, 155 and/or 143.

Overall patients with at least one raltegravir major mutation at raltegravir failure: 46/161 (28.6%)

Prevalence of patients harbouring raltegravir (RAL) resistance mutations at failure stratified by HIV-1 RNA load. The number (n) of patients is specified for each group. Resistance to raltegravir is defined by the presence of at least one major mutation in IN positions 143, 148 and 155.

Malet et al., JAC 2012
Prevalence of integrase sequences with at least 1 major raltegravir mutation from patients who had failed a regimen containing raltegravir according to viremia levels at failure

Overall proportion of samples with least one major raltegravir mutation at raltegravir failure: 54/156 (34.6%).

Santoro et al., ICAR 2014
Overall 36.4% of samples showed resistant GSS for raltegravir (and 28.3% for elvitegravir). By stratifying GSS scores according to viremia levels the proportion of samples showing raltegravir resistance significantly varied according with viremia levels (p=0.030)
Overall 36.4% of samples showed resistant GSS for raltegravir (and 28.3% for elvitegravir). By stratifying GSS scores according to viremia levels the proportion of samples showing raltegravir resistance significantly varied according with viremia levels (p=0.030)

High level resistance to dolutegravir was observed only in 2 samples (1.1%), both with a contextual HIV-RNA >1000 copies/mL: Q148K+G140A+E138K and Q148H+G140+G163G/R resistance mutations pattern, respectively

Armenia et al, JAC 2015
Impact of Low-Level-Viremia on HIV-1 Drug-Resistance Evolution among Antiretroviral Treated-Patients

Constance Delaugerre¹,²,³*, Sébastien Gallien²,³,⁴, Philippe Flandre⁵,⁶, Dominique Mathez⁷, Rishma Amarsy¹, Samuel Ferret⁴, Julie Timsit⁸, Jean-Michel Molina²,³,⁴, Pierre de Truchis⁹
Virologic failure was faster and more common in patients with lower genotypic susceptibility scores during low-level viraemia (LLV <1000 copies/ml)

There was a ‘dose-dependent’ increase in the hazard ratio for virologic failure with susceptibility categories at LLV.

These results demonstrate that emergent HIV drug resistance at LLV is strongly associated with subsequent virologic failure.

1702 patients with follow-up on constant therapy were eligible for the analysis

Kaplan–Meier curves for the proportion of patients remaining on the same therapy with viral loads <1000 copies/ml following their first low-level viraemia (LLV) episode. Patients are divided into four groups according to their GSS, and followed for up to 5 years while remaining on constant therapy.  

Swenson et al., AIDS 2014
Both subtherapeutic plasma drug levels and drug resistance increased the risk of subsequent virologic failure.
Patients with subtherapeutic plasma drug levels accumulated further drug resistance faster during follow-up.

Together, resistance and UDL variables can explain a higher proportion of virologic failure than either measure alone. Our results support further prospective evaluation of UDL in the management of low-level viremia.
Long-life treatment dictates the switch!!!

How we can personalize treatment switch in virologically suppressed patients?
HIV DNA Genotypic Resistance Test is a good tool for therapy optimization in both drug-naïve and drug-experienced patients

Increased requests of HIV DNA GRT in clinical practice over the recent years

Number of PBMCs genotypic resistance tests performed

- **Protease & Reverse Transcriptase**
- **Integrase**

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<table>
<thead>
<tr>
<th>Year</th>
<th>No. of sequences performed</th>
<th>No. of sequences performed</th>
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<tr>
<td>&lt;2004</td>
<td>23</td>
<td>14</td>
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<td>2015</td>
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<td>116</td>
</tr>
<tr>
<td>2016</td>
<td>182</td>
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</table>

*Armenia D unpublished data October 2016*
What about the impact of archived resistance in virologically suppressed patients that need a therapy switch?
Patients showing in PBMCs an intermediate or fully resistant GSS to the regimen administered had a higher probability of experiencing VR after therapy switching in treated patients with undetectable HIV-1 RNA compared to those showing full susceptibility.
Pre-existent NRTI and NNRTI resistance impacts on maintenance of virological suppression in HIV-1-infected patients who switch to a tenofovir/emtricitabine/rilpivirine single-tablet regimen

D. Armenia1†, D. Di Carlo1†, A. Calcagno2, G. Vendemiati2, F. Forbici3, A. Bertoli1, G. Berno3, S. Carta3, F. Continenza3, V. Fedele3, R. Bellagamba4, S. Cicalini4, A. Ammassari4, R. Libertone4, M. Zaccarelli4, V. Ghisetti2, M. Andreoni5, F. Ceccherini-Silberstein1, S. Bonora2, G. Di Perri2, A. Antinori6, C. F. Perno3 and M. M. Santoro1*

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†D. Armenia and D. Di Carlo equally contributed to this work.

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Objectives: To evaluate the maintenance of virological suppression (VS) in antiretroviral-treated HIV-1-suppressed patients switching to a tenofovir/emtricitabine/rilpivirine (TDF/FTC/RPV) single-tablet regimen, by considering pre-existent resistance (pRes).

Methods: pRes was evaluated according to resistance on all previous plasma genotypic resistance tests. Probability and predictors of virological rebound (VR) were evaluated.

Results: Three hundred and nine patients were analysed; 5.8% of them showed resistance to both NRTIs and NNRTIs, while 12.6% showed resistance to only one of these drug classes. By 72 weeks, the probability of VR was 11.3%. A higher probability of VR was found in the following groups: (i) patients with NRTI + NNRTI pRes compared with those harbouring NRTI or NNRTI pRes and with those without reverse transcriptase inhibitor pRes (39.2% versus 11.5% versus 9.4%, P < 0.0001); (ii) patients with a virus with full/intermediate resistance to both tenofovir/emtricitabine and rilpivirine compared with those having a virus with full/intermediate resistance to tenofovir/emtricitabine or rilpivirine and those having a virus fully susceptible to TDF/FTC/RPV (36.4% versus 17.8% versus 9.7%, P < 0.001); and (iii) patients with pre-therapy viraemia > 500 000 copies/mL compared with those with lower viraemia levels (> 500 000: 16.0%; 100 000–500 000: 9.3%; < 100 000 copies/mL: 4.8%, P = 0.009). pRes and pre-therapy viraemia > 500 000 copies/mL were independent predictors of VR by multivariable Cox regression.

Conclusions: TDF/FTC/RPV as a treatment simplification strategy shows a very high rate of VS maintenance. The presence of pRes to both NRTIs and NNRTIs and a pre-therapy viraemia > 500 000 copies/mL are associated with an increased risk of VR, highlighting the need for an accurate selection of patients before simplification.
Patients with pre-existent both NRTI+NNRTI resistance had a higher probability of experiencing virological rebound compared to those harboring pre-existent NRTI or NNRTI resistance and to those without pre-existent RTI resistance.

Overall probability of virological rebound 11.3%
Treatment should be individualized

Knowing the virological characteristics we can better identify patients eligible for a treatment simplification strategy.....
Clinical case: ID 10799

- Sex: man;
- Age: 48 years;
- Risk Factor: MSM;
- CDC: B;
- First HIV-1 seropositivity: 14 September 2010.
- Clinical data at first seropositivity response:
  - CD4: 448 cells/μl
  - VL: >10,000,000 cps/ml
  - Acute infection
- Clinical data on the 17th of September 2010:
  - CD4: 465 cells/μl
  - VL: 170,000,000 cps/ml
Clinical Case: ID 10799 Patient infected with HIV-1 B subtype

Age: 48  Sex: M  Risk Factor: MSM  CDC: B  1st Seropositivity: September-2010

Risk Factor: MSM
Clinical Case: ID 10799 Patient infected with HIV-1 B subtype

Age: 48  Sex: M  CDC: B  1st Seropositivity: September-2010

GRT 17 September 2010
VL: 170,000,000 cps/ml
CD4: 465 cells/ul
PR: L63A V77I
RT: V90I L100I K103N L210W T215D
Other PR-RT mutations
PR: I13V N37C D60E I62V
RT: V35I V60I A98S D121H K122E T139K I142V L159F Q197E A272P K277R I293V P294Q E297K Q334Y

GRT July 2015
VL: 184,933 cps/ml
CD4: 816 cells/ul
PR: L10F K20T V32I L33F K43T M46I I47V I54L L63P A71T V77I V82A L89V L90M I93L
RT: M41L K103N E138G Y181I
Other PR-RT mutations
PR: I13V K14R I15V N37E I66V C95F
RT: K20R E44D K49R V60I K122E D123N I135T V179I T286A I293V E297A

Undetectability threshold

Sep 10 – Mar 11
RAL MVC TDF/FTC DRV/r (800/100)

Apr 11 – Aug 11
RAL TDF/FTC DRV/r (800/100)

Sep 11 – Sep 12
TDF/FTC DRV/r (800/100)

Oct 12 – Jul 15
DRV/r (800/100)
Virological failure to a DRV/r (800/100) monotherapy in a patient infected with very high HIV RNA at baseline and a multi-resistant virus, with consequent emergence of resistance

Outcome 2016

Changed therapy with: DTG, FTC/TDF, MVC in September 2015

Last available follow-up (August 2016):
HIV-RNA: 302 copie/mL
CD4: 814 cells/mm³
Treatment simplification should be designed with caution: several factors can play a negative role on this strategy:

- **High pre-therapy viral load**
- **Low CD4 cells count**
- **Resistance**
- **Presence of blips**
Clinical case: ID 2502

- Sex: female
- Age: 50 years
- Risk Factor: Heterosexual
- First HIV-1 seropositivity: October 1999

Drugs received from December 1999 to November 2004:

NRTI: AZT 3TC D4T DDI
NNRTI: NVP
PI: IDV SQV
Clinical Case: ID 2502 Patient infected with HIV-1 B subtype
Risk Factor: Heterosexual
Age: 50
Sex: F
First Seropositivity: October 1999

- Genotyping Resistance Test on May 2004:
  CD4: 247 cells/µl; VL: 154,000 cps/ml

  PR: L63P
  RT: L41ML K103N L210LW T215NSTY
  INT: None

Other mutations
  PR: T4TS E35ED M36I N37ND I62IV I64L I93L
  RT: R83RK K122E I142IV K166KR R211K A272P K277R I293V
      E297A Q334N G335GD
  INT: V31I Q146QR T206S D207E T218S D256E A265AV

Drug treatment from December 2004 to January 2005:
3TC SQV/r LPV/r
Clinical Case: ID 2502 Patient infected with HIV-1 B subtype

<table>
<thead>
<tr>
<th>Age: 50</th>
<th>Sex: F</th>
<th>Risk Factor: Heterosexual</th>
<th>First Seropositivity: October 1999</th>
</tr>
</thead>
</table>

### Case Details
- **First Seropositivity:** October 1999
- **Age:** 50
- **Sex:** F
- **Risk Factor:** Heterosexual

#### Drug Regimens
- **DEC 04 – JAN 05:** 3TC SQV/r LPV/r
- **FEB 05 – DEC 05:** TDF 3TC EFV
- **JAN 06 – APR 12:** ATV/r TDF FTC
- **MAY 12 – MAY 17:** ATV/r 3TC

#### Virological Failure
- **GRT February 2005 from Plasma:**
  - **VL:** < 50 cps/ml
  - **CD4:** 374 cells/µl
  - **PR:** L63P
  - **RT:** None
  - **INT:** None

- **GRT May 2017 from Plasma:**
  - **VL:** 99 cps/ml
  - **CD4:** 1137 cells/µl
  - **PR:** M36I L63P I93L
  - **RT:** M41L K103N M184V T215Y

#### Virological Success
- **GRT May 2004 from Plasma:**
  - **VL:** 154,000 cps/ml
  - **CD4:** 247 cells/µl
  - **PR:** L63P
  - **RT:** L41ML K103N L210LW
  - **INT:** None

#### Drug Resistance
- **V3:** H13P T22A E25D I27V
- **Tropism:** R5
- **GRT May 2017 from Plasma:**
  - **PR:** M36I L63P I93L
  - **RT:** M41L K103N M184V T215Y

#### Virological Success
- **GRT February 2005 from Plasma:**
  - **VL:** < 50 cps/ml
  - **CD4:** 374 cells/µl
  - **PR:** L63P
  - **RT:** None
  - **INT:** None

#### Virological Failure
- **GRT May 2017 from Plasma:**
  - **VL:** 99 cps/ml
  - **CD4:** 1137 cells/µl
  - **PR:** M36I L63P I93L
  - **RT:** M41L K103N M184V T215Y

#### Risk Factors
- **Risk Factor:** Heterosexual

#### Clinical Case
- **Clinical Case:** ID 2502 Patient infected with HIV-1 B subtype
- **Age:** 50
- **Sex:** F
- **First Seropositivity:** October 1999

#### Geno2Pheno Algorithm
- **FPR:** 86.2%
Conclusions

- There is an increasing number of patients that maintain detectable levels of low/very low/residua viremia, and/or show blips of viral replication.
- The presence of low/very low/residua viremia is clinically relevant, being associated with an increased risk of virological failure.
- Current genotyping methods can recognize resistance also at viremia levels in the range of 50-500 copies/ml.
- The emergence of HIV drug resistance at LLV is strongly associated with subsequent virologic failure.
Conclusions

✓ The resistance genotyping should be encouraged for HIV-infected individuals on antiretroviral therapy experiencing low-level viraemia.

✓ All international guidelines focus on the importance of tailoring antiretroviral therapy to the individual patient, on the basis of HIV-1 genetic data, integrated with clinical, laboratory and therapeutic information.

✓ Making a correct and prompt diagnosis is fundamental for a correct therapeutic approach in all patients: when starting their first line regimen, at virological failure and in those switching therapy.
Thanks for your attention
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