Going the full 360: Benefits of optimal viral suppression

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Research grants from ViiV, Gilead, Merck, Johnson & Johnson.

Honorarium for consultation with ViiV, Gilead, Merck, Johnson & Johnson.
UNAIDS target: 90% of patients on ART virally suppressed

The treatment target

Diagnosed

On treatment

Virally suppressed

Virologic suppression: a confirmed HIV-1 RNA level below the LLOD of available assays

ART, antiretroviral therapy; LLOD, lower limit of detection.

To achieve optimal viral suppression, it is important to understand reasons for suboptimal suppression.

<table>
<thead>
<tr>
<th>Concepts associated with viral suppression</th>
<th>Causes of suboptimal viral suppression</th>
<th>Benefits of complete viral suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral load (VL) thresholds</td>
<td>Adherence</td>
<td>Avoid transmission</td>
</tr>
<tr>
<td>Virologic failure (VF)</td>
<td>Tolerability</td>
<td>Limit treatment resistance</td>
</tr>
<tr>
<td>Low level viremia (LLV)</td>
<td>Treatment resistance</td>
<td>Minimise chance of reactivation</td>
</tr>
<tr>
<td>Blips</td>
<td></td>
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</tr>
</tbody>
</table>

Clinical options for achieving and sustaining viral suppression

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LLV, low level viremia; VL, viral load; VF, virological failure.
Today, the goal of ART is to optimise virologic suppression is undetectable.

Antiretroviral drugs suppress HIV replication to undetectable levels after the start of therapy. HIV rebounds after cessation of therapy.

Active HIV replication

Limit of detection

Circulating virus

Time

ART, antiretroviral therapy; cp, copies.

Definition of virologic failure varies

Various definitions

• Confirmed plasma VL >50 cp/mL (France)¹

• Confirmed plasma VL >200 cp/mL (DHHS)²

• WHO guidelines for low-income and middle-income countries define virologic failure as one or more VL measurement of ≥1000 cp/mL³,⁴

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References:
Definition of persistent low-level viremia and very low-level viremia in HIV-1 infected patients

- **Very low-level viremia (1–20 cp/mL)**
- **Low-level viremia (50–500 cp/mL)**
- **VL > 500 cp/mL**


*HIV-1 RNA is detectable but not quantifiable using target detectable vs target not detectable (standard assays); Ultrasensitive Technique (SCA) in which quantification may also be used. ART, antiretroviral therapy; cp, copies; VL, viral load; ART, antiretroviral therapy; cp, copies; VL, viral load.

Residual viremia can persist for years in people on suppressive ART

- 40 PLHIV on suppressive ART (d4T + 3TC + LPV/r) followed for >7 years
- **Single-copy** assay revealed **77%** samples had detectable viremia (>1 cp/mL)
- **All participants** had at least one sample with detectable viremia

### HIV-1 RNA by single-copy HIV-1 RNA assay

<table>
<thead>
<tr>
<th>Years on ART</th>
<th>4</th>
<th>7</th>
<th>10</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetectable (&lt;1 cp/mL)</td>
<td>8 (44%)</td>
<td>10 (63%)</td>
<td>13 (76%)</td>
<td>5 (83%)</td>
</tr>
<tr>
<td>Detectable (≥1 cp/mL)</td>
<td>10 (56%)</td>
<td>6 (38%)</td>
<td>4 (24%)</td>
<td>1 (17%)</td>
</tr>
</tbody>
</table>

N=30 participants on suppressive ART from week 32 of initial therapy and for 10 or more years. ART included EFV + 2/3 NRTI (70%) or 2NRTI + 3rd agent (27%)

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**Detectable residual viremia is common among people on suppressive ART**

Suppressive ART defined as HIV-1 RNA <50 cp/mL
ART, antiretroviral therapy; cp, copies; d4T, stavudine; EFV, efavirenz; LPV, lopinavir; NRTI, nucleoside reverse transcriptase inhibitor; PLHIV, people living with HIV; /r, boosted with ritonavir; JTC, lamivudine

**Virological blips are infrequent for PLHIV on suppressive triple therapy combinations**

**Blips are VL >50 cp/mL preceded and followed by VL <50 cp/mL**

Viral blips were infrequent in treatment-naive adults treated with RPV/FTC/TDF or EFV/FTC/TDF through 96 weeks.

**Subjects who experienced blips compared with subjects with no blips by treatment group through week 96**

<table>
<thead>
<tr>
<th>Category</th>
<th>Overall (N = 717)</th>
<th>RPV/FTC/TDF (N = 365)</th>
<th>EFV/FTC/TDF (N = 352)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No blip</td>
<td>650 (90.7)</td>
<td>326 (89.3)</td>
<td>324 (92.0)</td>
</tr>
<tr>
<td>Blip</td>
<td>9.3%</td>
<td>10.7%</td>
<td>8.0%</td>
</tr>
<tr>
<td>P-value*</td>
<td></td>
<td>0.25</td>
<td></td>
</tr>
</tbody>
</table>

Viral blips are infrequent, and similar in both treatment groups and most PLHIV remained virally suppressed throughout the study to 96 weeks without virological failure.

*p-value for comparison between treatment groups
EFV/FTC/TDF; efavirenz/emtricitabine/tenofovir disoproxil fumarate; PLHIV, people living with HIV; RPV/FTC/TDF; rilpivirine/emtricitabine/tenofovir disoproxil fumarate; VF, virologic failure; VL, viral load.

Causes of suboptimal viral suppression
Potential causes of suboptimal viral suppression

- Insufficient drug level
- Viral replication in the presence of drug
- Resistant virus
- Treatment failure
- Poor adherence
- Social/personal issues
- Regimen issues
- Toxicities
- Transmission

- Suboptimal potency
- Wrong dose
- Host genetics
- Poor absorption
- Rapid clearance
- Drug interactions
- Number of drugs

References:
Reduced adherence to ART is associated with suboptimal viral suppression.

Mean adherence was 95%, showing a steady viral suppression can occur despite moderate ART non-adherence, but reduced adherence is associated with low-level residual viremia.
Lymph node and gut-associated lymphoid tissue are the principal sites of HIV replication and where the latent pool of virus is maintained.

Evaluation of INSTI levels in LN in HIV+ participants administered DTG (N=11), EVG/COBI (N=17), or RAL (N=6) with NRTIs

Samples analysed

- DTG: 13/17
- EVG/COBI: 19/26
- RAL: 4/6

In lymph nodes, only EVG/COBI achieved a median IQ >1

Further studies are needed to determine whether lower concentrations create conditions that allow persistent viral production.

ART concentrations in lymphatic tissues may influence viral suppression.
Consequences of suboptimal viral suppression
Consequences of sub-optimal viral suppression depend on the VL

ARV, antiretroviral therapy; LLV, low-level viremia; VL, viral load; VF, virologic failure; WHO, World Health Organization.


Consequences of VL above 200 cp/mL

†VL ≥1000 cp/mL

*Cohort of 782 patients in 37 centres in France with VL > 200 cp/mL exposed to a median of 6 antiretroviral drugs, including 2 NRTIs, 1 NNRTI, 3 PIs (IQR 2–4) and 0 INIs (IQR 0–1).


Risk of HIV transmission†

3 times higher risk of virologic failure† than people with VL <50 cp/mL

Detection of drug resistance in 57% of people with VL 201–500 cp/mL* under treatment²

Accumulation of drug resistance in cases of persistent viremia³
Higher VL is associated with increased risk of selection of integrase mutations

Association between the level of HIV VL at failure and selection of INSTI resistance-associated mutations in integrase

<table>
<thead>
<tr>
<th>HIV VL at failure (log cp/mL)</th>
<th>INSTI resistance-associated mutations in integrase</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3</td>
<td>58.60%</td>
</tr>
<tr>
<td>2–3</td>
<td>35.33%</td>
</tr>
<tr>
<td>&lt;2</td>
<td>5.96%</td>
</tr>
</tbody>
</table>

• Observational cohort of PLHIV failing on INSTI-containing regimen (2014 to 2017)

• At the time of failure, participants were on:
  – RAL (N=359)
  – EVG (N=154)
  – DTG (N=161)

• Treatment failure defined as two consecutive plasma VL >50 cp/mL

Note: bictegravir was not available at the time of the study
cp, copies; DTG, dolutegravir; EVG, elvitegravir; IN, integrase; INSTI, integrase strand transfer inhibitor; PLHIV, people living with HIV; RAL, raltegravir; RAM, resistance-associated mutation; VL, viral load; VF, virologic failure. Author’s own data provided with consent.
BIC and DTG were not associated with treatment emergent resistance in two randomised studies

**GS-1489/90: Multicenter, randomised, double-blind, active-controlled phase III trials of B/F/TAF vs DTG + 2NRTI**

B/F/TAF was statistically noninferior at the week 48 primary endpoint to regimens containing DTG in combination with a 2 NRTI backbone

- Primary endpoint: % achieving HIV-1 RNA < 50 cp/mL at week 48

1,274 participants included in a combined analysis of treatment emergent resistance

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<td>8 (1.3)b</td>
<td>2 (0.6)</td>
<td>3 (0.9)</td>
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<td>Confirmed virologic failure</td>
<td>2 (25, 0.3)</td>
<td>1 (50, 0.3)</td>
<td>1 (33, 0.3)</td>
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<tr>
<td>ESDD HIV-1 RNA of ≥200 copies/ml</td>
<td>5 (63, 0.8)</td>
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<td>2 (67, 0.6)</td>
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<td>Week 48 HIV-1 RNA of ≥200 copies/ml</td>
<td>1 (13, 0.2)</td>
<td>0</td>
<td>0</td>
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<td>Developed resistance substitutions to study drugs</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</table>

**Resistance analyses in 13 virologic failures found no treatment emergent resistance to study drugs**

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b The data are from studies: for B-F-TAF: 1489 and 1490; DTG-ABC-3TC: 1489; DTGF-TAF: 1490. Single percentage values are those for the group. b No participant on B-F-TAF had follow-up HIV-1 RNA data available at the time of this analysis, and therefore resuppression data were not available.

ABC, abacavir; B/F/TAF, BIC with emtricitabine and tenofovir alafenamide; BIC, bictegravir; DTG, dolutegravir; ESDD, early study drug discontinuation; INSTI-R, integrase strand transfer inhibitor resistance; NRTI, nucleoside reverse transcriptase inhibitor; NRTI-R nucleoside reverse transcriptase inhibitor resistance; NNRTI-R, non-nucleoside reverse transcriptase inhibitor resistance; PI-R, protease inhibitor resistance; RAP, resistance analysis population; 3TC, lamivudine.

Clinical management of virological failure

Determine the cause of VF, e.g.

- Patient/adherence-related factors (e.g. tolerance, pill burden)
- HIV-related factors (VL, resistance)
- ARV regimen-related factors (potency, low genetic barrier to resistance, DDI)

Therapeutic approach may differ depending on the cause of VF

Construct a new ARV regimen:

In case of resistance, at least two, preferably three, fully active drugs whose predicted activity is based on ART history, current and previous resistance test results, or a new mechanistic action

ARV, antiretroviral; DDI, drug-drug interactions; VL, viral load; VF, virological failure.

Consequences of low level viremia
(VL 50-200 cp/mL)

- No evidence of HIV transmission\(^1\)
- 2 times higher risk of virologic failure\(^\dagger\) than people with VL <50 cp/mL\(^2\)
- Detection of drug resistance in 50% of subjects under treatment\(^3\)
- Accumulation of drug resistance in cases of persistent low level viremia\(^4\)

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\(^{1}\) VL ≥1000 cp/mL.

\(^{2}\) VL, viral load; LLV, low-level viremia.

No evidence of HIV transmissions in condomless anal sex for people with VL <200 cp/mL

PARTNER2:

- No linked transmissions documented in ~77,000 condomless sex acts when HIV-positive MSM partner suppressed to VL < 200 cp/mL
- Unlinked transmissions occurred in 15 initially HIV-negative MSM partners

<table>
<thead>
<tr>
<th>Sexual Behaviour Reported by HIV-Negative Partner</th>
<th>Linked Transmissions, N</th>
<th>Upper 95% CI*</th>
<th>Condomless Sex Acts, N</th>
<th>CYFU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any sex</td>
<td>0</td>
<td>0.23†</td>
<td>76991</td>
<td>1596</td>
</tr>
<tr>
<td>Anal sex</td>
<td>0</td>
<td>0.24</td>
<td>70743</td>
<td>1546</td>
</tr>
<tr>
<td>Insertive anal sex</td>
<td>0</td>
<td>0.27</td>
<td>52572</td>
<td>1345</td>
</tr>
<tr>
<td>Receptive anal sex without ejaculation</td>
<td>0</td>
<td>0.43</td>
<td>23153</td>
<td>867</td>
</tr>
<tr>
<td>Receptive anal sex with ejaculation</td>
<td>0</td>
<td>0.57</td>
<td>20770</td>
<td>652</td>
</tr>
<tr>
<td>Any sex with an STI</td>
<td>0</td>
<td>2.74</td>
<td>6301</td>
<td>135</td>
</tr>
</tbody>
</table>

*For rate of within-couple HIV transmission per 100 CYFU. †Compared with 0.84 for MSM and 0.46 for heterosexuals in PARTNER1.
Increased risk of virologic failure with low-level viremia on ART

Effect of low-level viremia during ART on confirmed virologic failure in WHO-guided South African treatment programmes

All comparisons P<0.0001
Analysis for patients on first-line ART excluded 9242 patients with initial virologic failure, 17855 patients with one viral load result, and 1777 patients with less than 1 year of follow-up on ART, resulting in 40580 patients.

Confirmed virologic failure was defined as at least two viral load measurements of 1000 copies per mL or more without resuppression of first-line ART. All models included a random effect for province. Virologic suppression of less than 50 copies per mL was the reference value for low-level viremia. The increment for age was set at 5 years.

ART, antiretroviral therapy; cp, copies; LLV, low-level viraemia; PLHIV, people living with HIV; VL, viral load; VF, virologic failure; WHO, World Health Organization.

Drug resistance can develop in people with low level viremia on ART.

Participants were exposed to a median of 6 antiretroviral drugs (IQR 3–9), including 2 NRTIs (IQR 0–4), 1 NNRTI (IQR 0–1), 3 PIs (IQR 2–4) and 0 INIs (IQR 0–1). Ten percent were on first-line treatment.


Prevalence of HIV-1 drug resistance or possible resistance in treated patients with viral load more than 50 cp/mL in a 2014 French nationwide study

<table>
<thead>
<tr>
<th>HIV-RNAVL (cp/mL)</th>
<th>Prevalence (%) 2009</th>
<th>Prevalence (%) 2014</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1,000 cp/mL</td>
<td>69.5</td>
<td>57.8</td>
<td></td>
</tr>
<tr>
<td>501–1,000 cp/mL</td>
<td>78.1</td>
<td>61.0</td>
<td>0.009</td>
</tr>
<tr>
<td>201–500 cp/mL</td>
<td>61.2</td>
<td>56.8</td>
<td>0.039</td>
</tr>
<tr>
<td>VL &lt; 200 cp/mL</td>
<td>56.1</td>
<td>48.5</td>
<td>51–200</td>
</tr>
</tbody>
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Participants were exposed to a median of 6 antiretroviral drugs [IQR 3–9], including 2 NRTIs [IQR 0–4], 1 NNRTI [IQR 0–1], 3 PIs [IQR 2–4] and 0 INIs [IQR 0–1]. Ten percent were on first-line treatment. ART, antiretroviral therapy; cp, copies; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; INI, integrase inhibitor; PI, protease inhibitor; VL, viral load. Assoumou L et al. J Antimicrob Chemother 2017;72(6):1769–1773.
Clinical management of low level viremia

Multiple aspects must be considered:

• Modification of ART in cases of drug resistance to ongoing treatment

• TDM evaluation if suboptimal adherence or DDI is suspected

• Re-evaluation of the pharmacological classes used and strategies to improve adherence (e.g. reducing daily pill burden or choosing a STR)

• Due to the poor results of intensification treatment obtained thus far, adding drugs to classic triple therapy does not appear useful

• Otherwise, modification of the current ARV composition may improve its PK characteristics with the ultimate aim of obtaining complete virological control

ART, antiretroviral therapy; ARV, antiretroviral; DDI, drug-drug interactions; LLV, low-level viremia; PK, pharmacokinetic; STR, single tablet regimen; TDM, therapeutic drug monitoring.

Consequences of viral suppression (VL <50 cp/mL)

No evidence of HIV transmission

- Current evidence suggests that selection of drug-resistance mutations does not occur in patients with HIV RNA levels persistently suppressed to below the LLOD of current assays

No selection of drug resistance mutations

No risk of virological failure?

References:
2. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Available at: https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf [Accessed June 2019].
**Persistent HIV replication** in tissue sites, such as the lymph nodes, the GI tract, or **very low levels in plasma** detected with assays more sensitive than those used for clinical care, may be an important **driver of immune activation**.

Suggested mechanisms of HIV residual replication during ART:

- **Limited drug penetration** within tissues
- Presence of **immune sanctuaries**
- **Cell-to-cell** viral transmission
- Abnormal levels of **immune activation and inflammation**

**How low is low enough?**


ART, antiretroviral therapy.
Consequences of suboptimal viral suppression depend on VL: Key points

**Viral suppression**
- VL <50 cp/mL on ART
  - No evidence of HIV transmission
  - No emergence of drug resistance

**Low level viremia**
- VL 50 to 200 cp/mL
  - No consensus on how to manage these patients
  - Genotypic test and TDM could be considered

**Virologic failure**
- VL ≥200 cp/mL
  - Evidence of viral evolution and accumulation of drug-resistance mutations
- VL 1000 cp/mL (WHO definition of VF)
  - High risk of acquired resistance development\(^1\) especially for ARV with low genetic barrier

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ART, antiretroviral therapy; LLV, low-level viremia; TDM, therapeutic drug monitoring; VL, viral load; VF, virologic failure; WHO, World Health Organization.
Achieving and maintaining viral suppression
Theory predicts a lower probability of developing resistance to a 3-drug ARV combination

Probability of emerging resistant virus with 1, 2 or 3 ARV, considering that:

- New viruses made per day: $10^9$ to $10^{10}$
- Rate of spontaneous mutation: $10^{-4}$ to $10^{-5}$ per base, per cycle

Viral production > probability of spontaneous resistance emergence to 1 or 2 ARV → risk of resistance emergence

Viral production < probability of spontaneous resistance emergence to 3 or more ARV → lower risk of resistance emergence

BIC and DTG were not associated with treatment emergent resistance in two randomised studies

GS-1489/90: Multicenter, randomised, double-blind, active-controlled phase III trials of B/F/TAF vs DTG + 2NRTI\(^1\)

B/F/TAF was statistically noninferior at the week 48 primary endpoint to regimens containing DTG in combination with a 2 NRTI backbone

- Primary endpoint: % achieving HIV-1 RNA < 50 cp/mL at week 48

1,274 participants included in a combined analysis of treatment emergent resistance

### Treatment emergent genotypic resistance through week 48

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<td>0</td>
</tr>
<tr>
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<td>0</td>
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<td>0</td>
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</tbody>
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\(^a\)The data are from studies: for B-F-TAF: 1489 and 1490; DTG-ABC-3TC: 1489; DTGF-TAF: 1490. Single percentage values are those for the group. \(^b\)No participant on B-F-TAF had follow-up HIV-1 RNA data available at the time of this analysis, and therefore resuppression data were not available.

ABC, abacavir; B/F/TAF, BIC with emtricitabine and tenofovir alafenamide; BIC, bictegravir; DTG, dolutegravir; ESDD, early study drug discontinuation; INSTI-R, integrase strand transfer inhibitor resistance; NRTI, nucleoside reverse transcriptase inhibitor; NRTI-R nucleoside reverse transcriptase inhibitor resistance; NNRTI-R, non-nucleoside reverse transcriptase inhibitor resistance; PI-R, protease inhibitor resistance; RAP, resistance analysis population; 3TC, lamivudine.


Resistance analyses in 13 virologic failures found no treatment emergent resistance to study drugs
Switch to 2DC was non-inferior to continuation of baseline ART in virologically-suppressed adults

SWORD-1 and -2: Parallel, randomised, open-label, multicenter phase III noninferiority studies

At week 48, DTG + RPV was non-inferior (~8% margin) to continuing current three drug regimen

Adults on stable ART (INSTI, NNRTI, or PI + 2 NRTIs*) with HIV-1 RNA < 50 cp/mL for ≥ 6 months at screening; no previous VF or current HBV infection (N = 1024)

Virologic outcomes persisted through 148 weeks after switch to 2DC

**SWORD-1 and -2**

- DTG + RPV virologic outcomes were sustained 148 weeks after switch\(^1\)
- Safety profile of late-switch DTG + RPV following 100 weeks of therapy similar to the early-switch group at week 100
- 11 confirmed virologic withdrawals (1%; 11/990) at 148 weeks\(^1\)
  - No INSTI resistance was observed
  - Limited resistance to RPV in 5 people (0.5%); 1 of whom had pre-existing NNRTI RAMs

<table>
<thead>
<tr>
<th>HIV-1 RNA &lt;50 cp/mL at Weeks 48, 100 and 148</th>
<th>Virologic success as measured by HIV-1 RNA &lt;50 cp/mL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early switch group (N=513)</td>
<td></td>
</tr>
<tr>
<td>DTG + RPV, Day 1 to week 48</td>
<td>95</td>
</tr>
<tr>
<td>DTG + RPV, Day 1 to week 100</td>
<td>89</td>
</tr>
<tr>
<td>DTG + RPV, Day 1 to week 148</td>
<td>84</td>
</tr>
<tr>
<td>Late switch group (N=477)</td>
<td></td>
</tr>
<tr>
<td>DTG + RPV, week 52 to week 100</td>
<td>93</td>
</tr>
<tr>
<td>DTG + RPV, week 52 to week 148</td>
<td>90</td>
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Sustained virologic outcomes and limited emergence of resistance seen at 148 weeks in patients switched from suppressive ART to 2DC

Bl, baseline; cp, copies; DTG, dolutegravir; INSTI, integrase strand transfer inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; RAM, resistance-associated mutation; RPV, rilpivirine; 2DC, two drug combination.

Clinical consequences of failing 2DC compared with triple therapies

- Genotypic resistance testing was performed at the time of first VF in:
  - 200 consecutive patients failing triple therapy (PI or INI-based)
  - all patients failing 2DC (PI and/or DTG-containing regimen)
- VF was defined as the occurrence of two consecutive VL > 50 cp/mL
- INI TT included RAL, EVG/cobi and DTG based regimens.
  - PI TT included DRV/r and ATV/r based regimens.
  - DTG 2DC included DTG+3TC and DTG+RPV.
  - PI 2DC included PI + RAL, DTG or 3TC.

Emergent resistance among patients on 2DC or triple therapy ART without previous virologic failures

<table>
<thead>
<tr>
<th></th>
<th>% patients with emergent resistance</th>
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<tr>
<td>PI TT (N=100)</td>
<td>3</td>
</tr>
<tr>
<td>INI TT (N=100)</td>
<td>7</td>
</tr>
<tr>
<td>DTG 2DC (N=23)</td>
<td>21.7</td>
</tr>
<tr>
<td>PI 2DC (N=32)</td>
<td>37.5</td>
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Higher rates of drug resistance selection observed in patients failing a DTG- or PI-containing 2DC compared to INI- or PI-containing triple therapy (3 fold and 12.5 fold, respectively)

Conclusions: Benefits of optimal viral suppression

Newer drugs show a higher rate of virological success with no treatment emergent resistance\(^1\)\(^-\)\(^4\)

Clinical evidence has found 2DC to be non-inferior to triple therapy for maintaining viral suppression\(^5\)\(^,\)\(^6\)

While some evidence suggests optimal viral suppression (VL < 50 cp/mL on ART) is associated with a reduced risk of:\(^1\)\(^-\)\(^4\)

- Resistance-associated mutations
- Viral transmission
- Virologic failure

Some evidence suggests increased rate of drug resistance selection with 2DC compared to triple therapy\(^7\)

Real-world clinical scenarios are often more complex than clinical trials, which may affect approach to viral suppression:\(^2\)\(^,\)\(^8\)

- Poor or inconsistent adherence with ART
- Unclear treatment history
- Archived resistance-associated mutations

Durable suppression is a key consideration for treatment selection as it is essential for long-term outcomes

ART, antiretroviral therapy; cp, copies; VL, viral load; 2DC, two drug combination.

- AIDSInfo. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Available at: https://aidsinfo.nih.gov/guidelines