# The Virostar study: Analysis of emergent resistance-associated mutations at first- or second-line HIV-1 virologic failure with second generation InSTIs in 2- and 3-drug regimens

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## BACKGROUND

- During the last 30 years, ARV regimens for human immunodeficiency virus (HIV) infection has been continuously evolving. The effectiveness of latest-generation 3DRs allowed a dramatic increase in the life expectancy of HIV-infected patients, although it was associated with several side effects and treatment-related toxicities[1]. Nevertheless, in case of VF, a treatment-emergent resistance to an ARV can limit a patient's options for future therapy, prompting the need for ART that are resilient to the emergence of resistance[2,3,4].
- DTG or BIC, both second generation InSTIs with high genetic barrier against resistance and potent antiretroviral activity, were evaluated in 3DRs in large phase 3 clinical trials and both showed limited side-effects and drug-drug interactions, improved treatment compliance and zero emerging RAMs at VF in treatment-naive populations. Recently DTG was also evaluated in 2DRs in clinical trials and showed only 2 cases of emerging RAMs to DTG in treatment-naive populations. Both BIC- or DTG-based 3DRs and DTG-based 2DRs are currently recommended as initial* or switch options in DHHS, IAS-USA and EACS international guidelines[2,3,4,5,6,7,8].
- We postulate emerging RAMs at VF could be different in a real life setting between BIC- or DTG-based 3DRs and DTG-based 2DRs, with the lowest emerging RAM rate to be found with BIC/FTC/TAF. Thus, we conducted a national, multicenter, retro-prospective observational study to measure emerging RAM rates in patients failing their ART (VF) in a first- or second-line ART with BIC/FTC/TAF, DTG/ABC/3TC, DTG+3TC or DTG+RPV*.

## MATERIALS AND METHODS

- Retrospective observational study including several centers in France. Study period was 2019-2021. Virological failure (VF) was defined as the occurrence of two consecutive HIV-1 plasma viral loads > 50 copies/ml.
- Sanger genotypic resistance assays were performed during standard clinical care at the time of a first- or second-line VF in blood plasma samples from patients failing their ART.
- The primary objective was to measure emerging RAM rates in patients failing their ART (VF) in a first- or second- line ART with BIC/FTC/TAF, DTG/ABC/3TC, DTG+3TC or DTG+RPV*, regardless of wether these regimens were taken as STR or MTR.

## RESULTS (Table 1)

- 4328 patients were in a first- or second-line ART during the study period: 49,5% (n=2141) with BIC/FTC/TAF; 33.1% (n=1435) with DTG/ABC/3TC; 10.4% (n=452) with DTG+3TC; 6.9% (n=298) DTG+RPV.
- The observed VF rates in these patients were: 7% (n=150) for BIC/FTC/TAF; 8.1% (n=117) for DTG/ABC/3TC; 6% (n=27) for DTG+3TC; and 5% (n=15) for DTG+RPV.
- The total emerging RAMs at VF in these patients were:
  - 4.7% (n=7) for BIC/FTC/TAF (n=2 InSTI RAMs + n=5 NRTI RAMs);
  - 7.7% (n=9) for DTG/ABC/3TC (n=2 InSTI RAMs + n=7 NRTI RAMs);
  - 18,5% (n=5) for DTG+3TC (n=1 InSTI RAMs + n=4 NRTI RAMs);
  - 40% (n=6) for DTG+RPV (n=6 NNRTI RAMs).

## DISCUSSION

- We found that in real world setting the rate of VF defined as two consecutive HIV-1 plasma viral loads > 50 copies/ml was overall low in patients receiving 2nd generation InSTIs (BIC/FTC/TAF, DTG/ABC/3TC, DTG+3TC and DTG+RPV).
- The lowest total emerging RAM rate at VF was found with BIC/FTC/TAF. The highest total emerging RAM rate at VF was found with DTG+RPV.
  - Uncommon (< 4%) emerging InSTI RAMs were detected in patients failing BIC- or DTG-based 3DRs or DTG-based 2DRs in a first- or second-line ART.
  - Few (< 15%) emerging NRTI RAMs were detected in patients failing BIC- or DTG-based 3DRs or DTG+3TC. in a first- or second-line ART.
  - More emerging NNRTI RAMs were detected at VF with DTG+RPV.

**Table 1: Emerging RAM rates during the study period in patients failing their ART (VF) in a first- or second-line ART (N=4328)**

| Regimens | BIC/FTC/TAF n=2141 | DTG/ABC/3TC n=1432 | DTG+3TC n=452 | DTG+RPV* n=298 |
|---|---|---|---|---|
| Patients with VF | 7%, n=150 | 8.1%, n=117 | 6%, n=27 | 5%, n=15 |
| **Total emerging RAMs at VF** | **4.7%,** n=7 | **7.7%,** n=9 | **18.5%,** n=5 | **40%,** n=6 |
| *Emerging InSTI RAMs* | *1.3% n=2*<br>*1 E138K;*<br>*1 Y143C.* | *1.7%, n=2*<br>*1 G140S+Q148H;*<br>*1 E92Q* | *3.7%, n=1*<br>*1 N155H* | *0%, n=0* |
| *Emerging NRTI RAMs* | *2.5%, n=5*<br>*5 M184V.* | *6%, n=7*<br>*6 M184V;*<br>*1 M184I.* | *14.8%, n=4*<br>*4 M184V.* | *N/A* |
| *Emerging NNRTI RAMs* | *N/A* | *N/A* | *N/A* | *40%, n=6*<br>*3 E138A;*<br>*1 M230L;*<br>*1 K101E;*<br>*1 Y181C.* |

## REFERENCES

* DTG+RPV regimen in not recommended in a first line ART[2,3,4].

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## ABBREVIATIONS

**2DR**: Two-drug regimens; **3DR**: Three-drug regimens; **3TC**: Lamivudine; **ABC**: Abacavir; **ART**: antiretroviral treatment; **BIC**: Bictegravir; **DHHS**: Department of Health and Human Services; **DTG**: Dolutegravir ; **EACS**: European AIDS Clinical Society; **FTC**: Emtricitabine; **IAS-USA**: International Antiviral Society-USA; **InSTIs**: Integrase strand transfer inhibitors; **MTR**: Multiple tablet regimen; **NRTI**: Nucleoside Reverse Transcriptase Inhibitor; **NNRTI**: Non-Nucleoside Reverse Transcriptase Inhibitor; **RAM**: Resistance associated mutation; **RPV**: Rilpivirine; **STR**: Single tablet regimen; **TAF**: Tenofovir alafenamide; **VF**: Virologic failure.

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