HIV RESISTANCE TO ART

Update on HIV resistance and its impact on our current (and future) practice

Gilles Darcis Nov 28, 2024

PLAN: HOT TOPICS

- DTG
- Long-Acting Cabotegravir and Rilpivirine Injectable Therapy

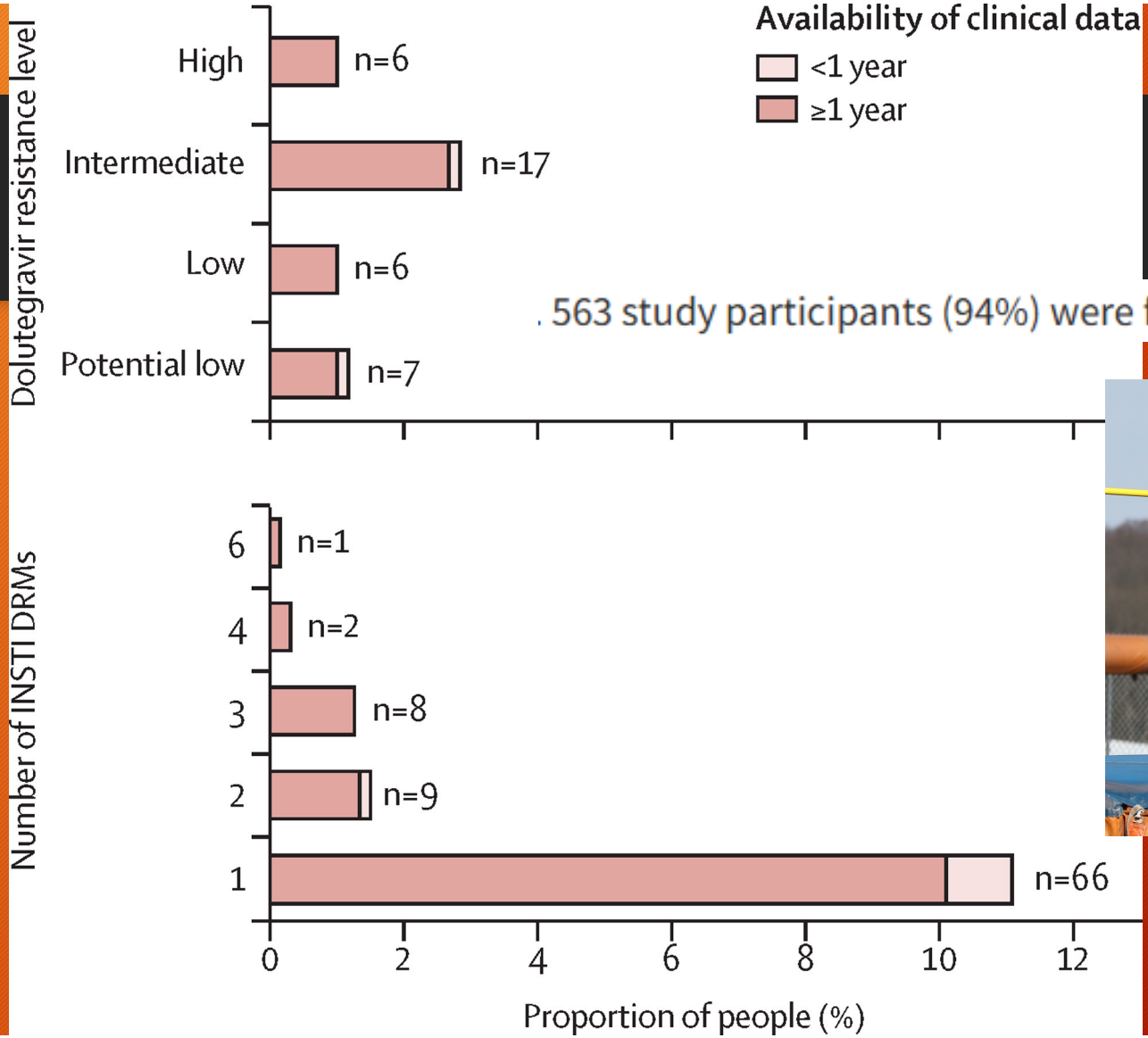
HIV-1 drug resistance in people on dolutegravir-based antiretroviral therapy: a collaborative cohort analysis

Tom Loosli, Stefanie Hossmann, Suzanne M Ingle, Hajra Okhai, Katharina Kusejko, Johannes Mouton, Pantxika Bellecave, Ard van Sighem, Melanie Stecher, Antonella d'Arminio Monforte, M John Gill, Caroline A Sabin, Gary Maartens, Huldrych F Günthard, Jonathan A C Sterne, Richard Lessells, Matthias Egger*, Roger D Kouyos**

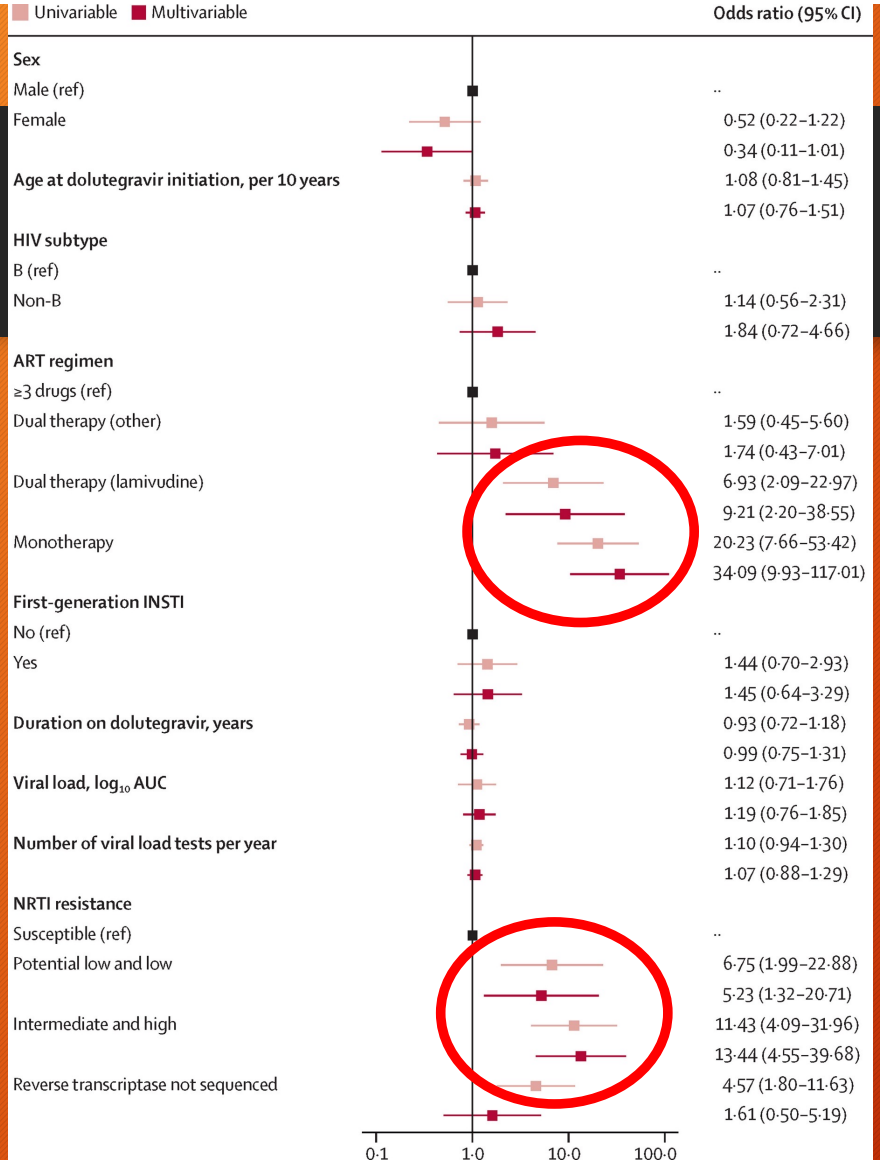
THE LANCET HIV

- DTG **RESIST** study combined data from HIV cohorts to examine
  - Level / patterns of drug resistance mutations (DRMs)
  - identify risk factors for dolutegravir resistance.
- 599 study participants (real-world data from different settings) **viraemic on dolutegravir-based ART**
- Most participants were men living with HIV-1 subtype B

Volume 10, Issue 11, E733-E741, November 2023



. 563 study participants (94%) were fully susceptible to dolutegravir



LIMITATIONS:

Genotypic resistance testing before starting or switching ART might have prevented some individuals from receiving dolutegravir

Dominance of HIV-1 subtype B

Duration of viraemia while receiving dolutegravir were relatively short

WHO : DTG resistance in resource-limited settings?

- ART regimens are highly standardized (TLD)
- Drugs are recycled
- Access to adherence support limited
- Viral load and resistance testing is (very) limited
- Risk for drug stock-outs higher
- DDI (rifampicin use)

Table 4. HIV drug resistance to DTG among adults receiving DTG-based ART in PEPFAR-supported surveys, 2020–2022

Country	Method	Sample size genotyped	Inclusion criteria	Year of sample collection	Prevalence of DTG resistance
Uganda	Laboratory-based	457 (255 amplified)	• At least nine months on a DTG-based regimen • Dried blood spots or plasma test with viral load ≥1000 copies/mL • ≥15 years of age	2021–2022	3.9%[a]
Ukraine	Laboratory-based	366 (315 amplified)	• At least nine months on a DTG-based regimen • Plasma viral load ≥1000 copies/mL • >18 years of age	2020–2021	
Mozambique	Clinic-based	193 (183 amplified)	• Treatment-experienced people transitioned to TLD experienced persistent failure to suppress viral load (viral load >1000 copies/mL) • >18 years of age	2021–2022	
Malawi	Clinic-based	213 (212 amplified)	• At least nine months on a DTG-based regimen • Viral load ≥1000 copies/mL • ≥15 years of age	2020–2021	8.6%[a]

PLAN

- DTG
- **Long-Acting Cabotegravir and Rilpivirine Injectable Therapy**

QUESTION 1: GENETIC BARRIER OF CAB/RPV?

Virological Failure After Switch to Long-Acting Cabotegravir and Rilpivirine Injectable Therapy

- The virological efficacy of LA CAB/RPV was assessed in multiple randomized clinical trials
- **Low risk** (1.4%) for confirmed VF

BMI / Subtype A6 / RPV DRM

Clin Infect Dis. 2023 Jun 21;77(10):1423–1431

- Limited data from few realworld cohorts, confirming high efficacy rates as observed in the trials
- **Selection of resistance-associated mutations**
- Uncertainty on the reasons behind the failure

Infect Dis Ther 2023; 12:2807–17
Clin Infect Dis 2023; 76:e645–51
AIDS 2023; 37:605–9.

N Engl J Med 2020; 382: 1124–35.
Lancet HIV 2021; 8:e668–78
Lancet HIV 2021; 8:e185–96
Lancet 2021; 396:1994–2005
Clin Infect Dis 2023; 76:1646–54
N Engl J Med 2020; 382: 1112–23
Lancet HIV 2023; 10:e566–77

INTEGRASE STRAND TRANSFER INHIBITOR (INSTI) RESISTANCE

HIV DRUG THERAPY GLASGOW 2024

CAB drug resistance

Line of treatment	N	Genotyped	% CAB resistant
First-Line	513	6	5 (71%)
Switch suppressed	5703	26	18 (64%)
2nd line viraemic	987	18	6 (39%)

Andrew Hill

QUESTION 2: CAB/RPV

Do you inform your patient of a higher risk of VF and emergence of resistance, with possible consequences on U=U, with injectables CAB/RPV compared with DTG- or BIC-based oral ART?

December 1, 2022

Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults

2022 Recommendations of the International Antiviral Society–USA Panel

Even among patients who receive all of the scheduled injections in a timely fashion, there is a risk of treatment failure with emergent resistance, including both InSTI and NNRTI mutations in some. Although this risk is small (approximately 1%-2% in clinical trials), it is higher than for continued oral ART with dolutegravir- or bictegravir-based regimens, and patients should be informed of this risk prior to switching to long-acting injectable ART. The risk appears to be higher when giving cabotegravir plus rilpivirine every 8 weeks than every 4 weeks. Treatment options for those who experience treatment failure with long-acting cabotegravir plus rilpivirine and develop resistance will be limited, because neither NNRTI-based nor InSTI-based regimens are optimal choices.

JAMA. 2023;329(1):63-84. doi:10.1001/jama.2022.22246

5.12 Two-drug injectable regimens: switching in virological suppression

- We recommend that long-acting cabotegravir/rilpivirine can be used in people who:
  - Face challenges taking daily oral ART (GPP) *and*
  - Have been virally suppressed to <50 copies/mL for at least 6 months (Grade 1A) *and*
  - Have no known or suspected NNRTI or INSTI resistance (Grade 1A) *and*
  - Have no history of virological failure or unplanned treatment interruption on NNRTI- or INSTI-containing ART (Grade 1A) *and*
  - Have no history of INSTI monotherapy (GPP) *and*
  - Can commit to 2-monthly attendance for injections (GPP) *and*
  - Accept the risk of virological failure and resistance despite complete adherence and the potential implications for U=U (GPP) *and*
  - Have a body mass index (BMI) of <30 kg/m^2 AND non-A1/6 subtype if baseline resistance is unavailable (Grade 1A) *and*
  - Do not need a tenofovir containing regimen for the treatment or prevention of hepatitis B (Grade 1A).

QUESTION 3: VL monitoring (CAB/RPV)

1) 2x/year (1x/3 injections)
2) 3x/year (1x/2 injections)
3) 6x/year (at each visit/injection)
4) another

VL monitoring: how often?

BHIVA
British HIV Association

BHIVA guidelines on antiretroviral treatment for adults living with HIV-1 2022

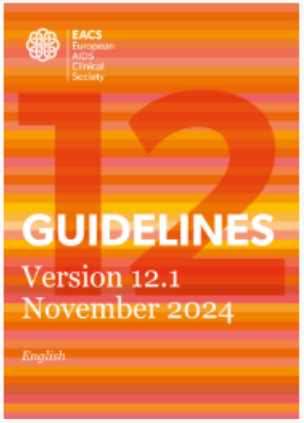
- Do not need a tenofovir containing regimen for the treatment or prevention of hepatitis B (Grade 1A).

- We recommend that long-acting cabotegravir/rilpivirine can be continued in people who:
  - Have received long-acting cabotegravir/rilpivirine in a clinical trial (GPP);
  - Are on long-acting cabotegravir/rilpivirine as part of a compassionate access or named patient programme (GPP).

- We recommend the following viral load monitoring:
  - Two-monthly HIV RNA quantification (Grade 1A);
  - Prompt recall for repeat testing and resistance testing if viral rebound occurs (GPP).

1A
Strong recommendation
High-quality evidence

EACS Guidelines 2024



Long-acting intramuscular dual therapy CAB + RPV

- The use of oral lead-in (1 month) is optional
- Injections are administered every 2 months. In case of bridging, see the section on Drug-Drug Interactions after Oral and Intramuscular Administration of CAB and RPV

Initiation phase (start on day of last oral pills)	Continuation phase
Day 0: CAB 600 mg/ RPV 900 mg Month 1: CAB 600 mg/ RPV 900 mg	From month 2 onwards: CAB 600 mg/ RPV 900 mg every 2 months

The following baseline factors, when combined, are associated with risk of virologic failure and resistance:

- Archived RPV-associated mutations
- HIV subtype A6/A1 (Recent data suggest possible use in people with subtype A1)
- BMI ≥ 30 kg/m^2

Dear Gilles,

Thanks a lot for your question.

Indeed, this was a point for discussion within the ART section. Finally, we decided not to include any specific comment, since in the initial table for monitoring,

https://eacs.sanfordguide.com/eacs-part1/assessment-hiv-positive-persons-at-initial-subsequent-visits

Image supprimée par l'expéditeur.

1: Assessment of Initial & Subsequent Visits

/

eacs.sanfordguide.com

the range is 3-12 months and we considered CAB-RPV could also be monitored that way (see enclosed screeshot).

You are right, Bristish Guidelines are the more conservstive in this specific point. In my opinion, at the moment there were reviwing this topic only the trials were published, with very limited real-world data to support other recommendation. I also think people monitor CAB-RPV very differently. In our clinic, we add a VL at M3, then M6 and then every 6 M.

CC'd are the leads for ART section, in case they want to add more info.

Best regards,

Juan Ambrosioni
Guidelines Coordinator

JOURNAL ARTICLE

Virological Failure After Switch to Long-Acting Cabotegravir and Rilpivirine Injectable Therapy: An In-depth Analysis

Berend J van Welzen, Steven F L Van Lelyveld, Gerjanne Ter Beest, Jet H Gisolf, Suzanne E Geerlings, Jan M Prins, Gitte Van Twillert, Cees Van Nieuwkoop, Marc Van der Valk, David Burger, Annemarie M J Wensing

Clinical Infectious Diseases, Volume 79, Issue 1, 15 July 2024, Pages 189–195, https://doi.org/10.1093/cid/ciae016

3 of the 5 cases had no known risk factors at baseline; the others had only high BMI

All cases acquired NNRTI RAMs and in 4 cases there was also selection of INSTI RAMs

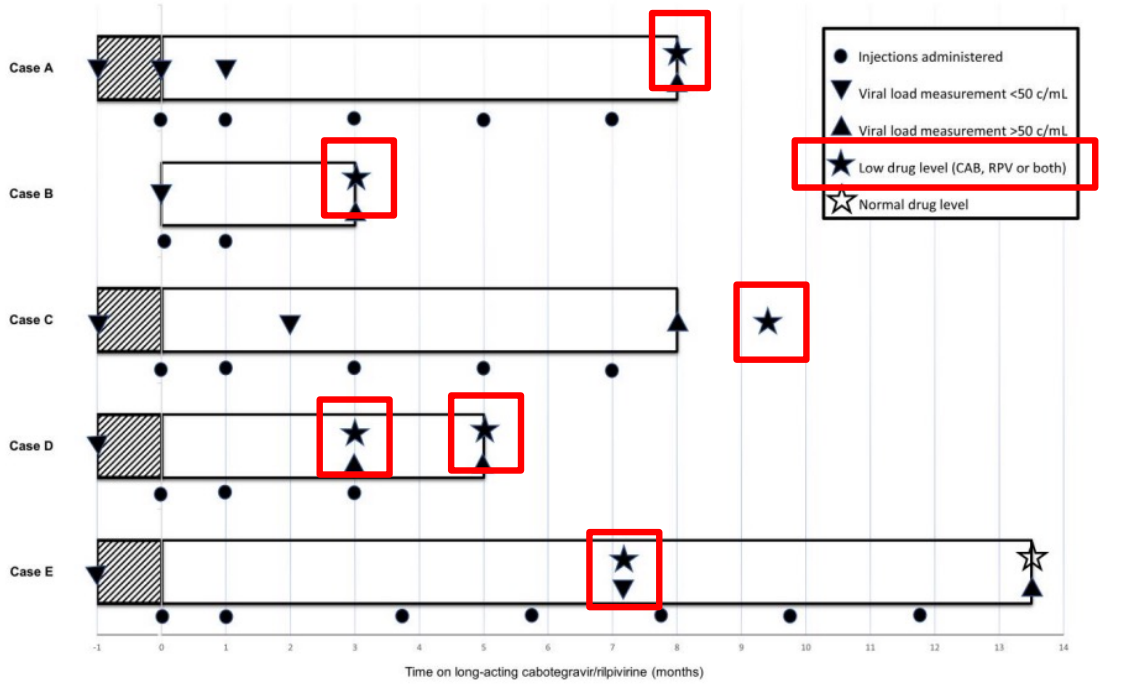


Figure 1. Cabotegravir (CAB) plus rilpivirine (RPV) treatment trajectories of the 5 cases from start to discontinuation. The symbols illustrate the timing of injection administration, viral load (copies/mL), and drug level measurement. The shaded area represents the oral lead-in period of 28 days.

ANALYSIS

- **CASE A**: Patient's body mass index **(BMI) increased** from 29.0 to 33.5 kg/m2 during the treatment course, the needle length was not adjusted.
- **CASE B**: findings were suggestive for a **problem with the administration** of 1 of the CAB injections during the loading phase
- **CASE C**: low CAB. No reason for these pharmacokinetic findings could be identified
- **CASE D**: no factors for the consistently low CAB and RPV levels could be identified
- **CASE E**: **prolonged dosing interval** between the second and third series

Risk of VF and resistance to CAB/RPV

- It is important to consider baseline risk factors (NNRTI exposure?)
- Also to continuously reconsider evolving risks
- Intensified VL monitoring depending on patient's profile?

Thank you

P088

Virological failure rate and emergent resistance in real-world studies evaluating long-acting cabotegravir and rilpivirine in people with baseline viral suppression

Melanie Smuk, Alexa Elias, Kyle Ring, Chloe Orkin
SHARE Collaborative, Queen Mary University of London, Blizard Institute, London, UK

- Synthesis on a systematic literature review conducted from January 2020 to March 2024 on RWE use of CAB+RPV for treatment.
- 27 studies with available data on VF, including **5048** individuals who were virally suppressed at switch.
- The duration of follow-up varied greatly (range 1-24 months) and thus estimating a pooled VF rate across studies would be **uninterpretable** due to the heterogeneity between studies

Conclusions: Calculating an accurate VF rate using RWE is difficult due to heterogeneity of VF definition and study design. Resistance emerged commonly where VF occurred.

P088: Table 1. Emergent resistance data available on people who experienced VF in RWE[a]

Participants with VF	Emergent resistance? (No/NNRTI/INI)	Mutations
1	NNRTI + INI	(Y181C) + (L74I, T97A, E138K, Q148R and N155H)
2	NNRTI	K103N, L100I
3	No	NA
4	No	NA
5	No	NA
6	NNRTI + INI	(L100I, K103NS) + (E138KA, G140SAC, Q148HRK)
7	NNRTI	M230L, V179E
8	NNRTI	E138A, V179I
9	No	NA
10	No	NA
11	No	NA
12	NNRTI + INI	(101E+138K+230L) + (155H)
13	NNRTI + INI	(101E+138K) + (138K+148R)
14	NNRTI	E138A
15	NNRTI + INI	(L74L/M, T97T/A) + (G140S, Q148H, K101P, E138K, I178L, Q207E)
16	INI	L74I, T97T/A, S147S/G, N155H
17	INI	G140G/S, Q148Q/R
18	NNRTI + INI	(K101E, N348I) + (E138A, G140S, Q148S)
19	NNRTI + INI	(Y188L) + (Q148R)
20	NNRTI + INI	(K101E, I178M) + (N155H, R263K)
21	No	NA
22	NNRTI	K103N, E138Q
23	NNRTI	K103K/R, E138G/R
24	NNRTI + INI	(M230M/L) + (E138E/K, Q148Q/K)
25	No	NA
26	No	NA
27	No	NA

[a]We included studies where relationship between drug class and emergent mutations was specified.