Prevalence and factors associated to the detection (population and next generation sequencing) of archived 3TC resistance mutations in aviremic HIV-infected adults (GEN-PRO)

Rocio Montejano [1], Lourdes Dominguez-Dominguez [2], Andres Esteban-Cantos [1], Monica Garcia [2], Natalia Stella [1], Otilia Bisbal [2], Rosa De Miguel [1], David Rial [2], Paula Araguren [2], J Ignacio Bernardino [1], J Miguel Castro [1], Laura Bermejo [2], Mario Mayoral [1,] Mireia Santacreu [2], Belen Alejos [3], Rafael Delgado [2], Rafael Rubio [2], Jose R Arribas [1], Federico Pulido [2],
Gen-Pro, PI16/00837 - PI16/00678 Study Group

[1]Hospital Universitario La Paz - IdiPAZ, Madrid, [2]Hospital Universitario 12 de Octubre - Imas12, Madrid, [3]Instituto de Salud Carlos III, Madrid,

PURPOSE

- To evaluate in aviraemic patients the frequency of re-detection of M184V/I and K65R/E/N mutations in proviral DNA (pDNA) by population sequencing (PS) and next generation sequencing (NGS), the concordance between both techniques and predictive factors for clearance of M184V/I-K65R/E/N.

METHODS

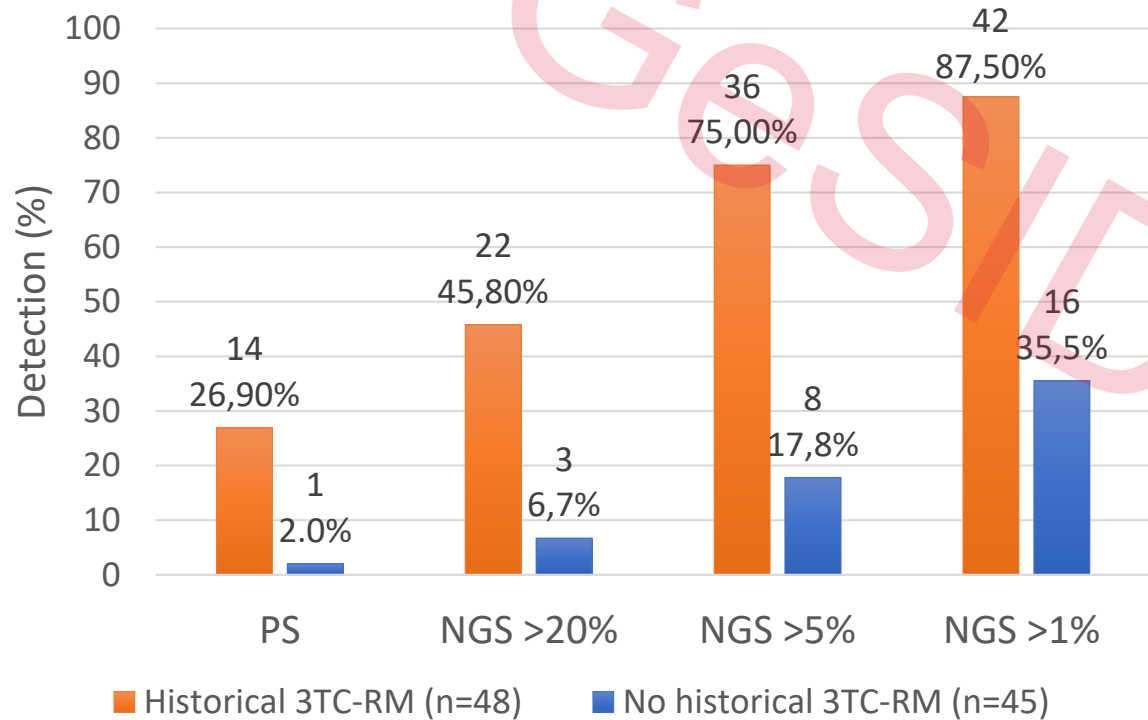- Observational, cross-sectional study.

- Resistance mutations (RM) were identified and quantified using PASeq system (IrsiCaixa).

PARTICIPANTS CHARACTERISTICS

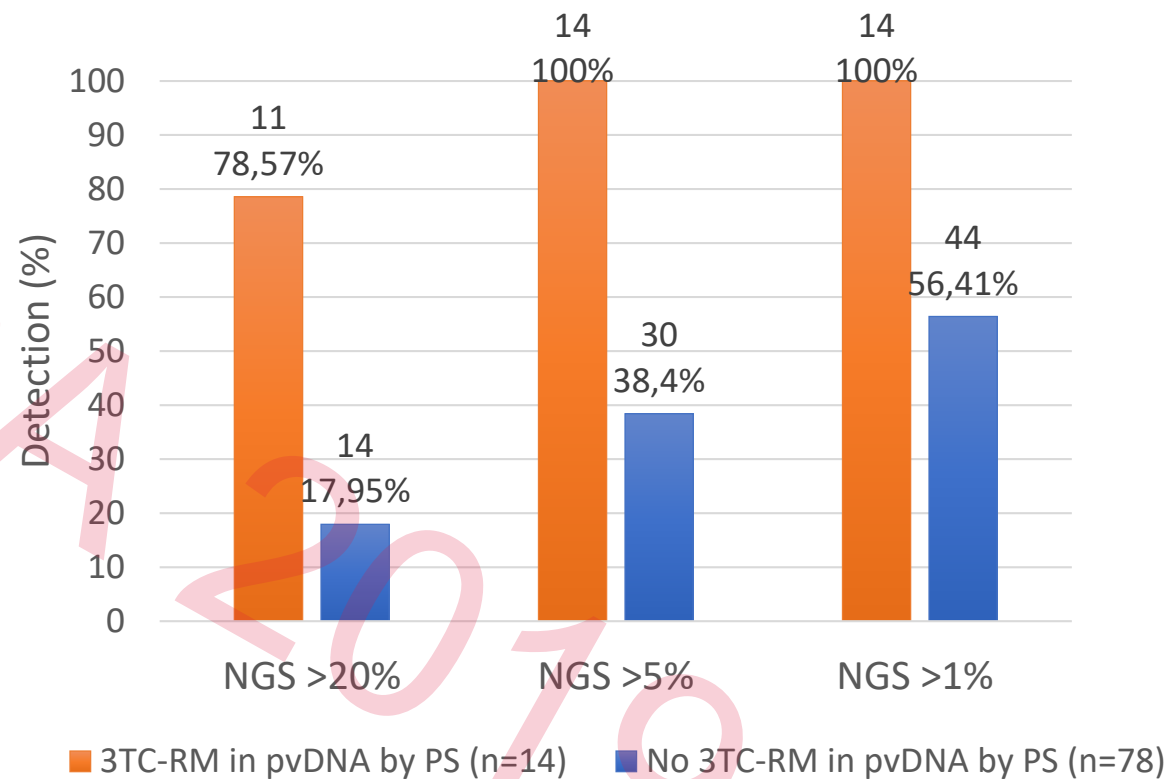| N=102	Historical M184V/I and/or K65R/E/N (n=52)	No historical M184V/I and/or K65R/E/N (n=50)	p value
Male sex, n (%)	36 (69.2)	41 (82.0)	NS
Age (years), median (IQR)	52.2 (49.0–58.4)	47.6 (41.8–54.2)	**0.017**
Intravenous drug user, n (%)	17 (32.7)	7 (14.0)	**0.028**
Years since HIV diagnosis, median (IQR)	21.9 (17.5–24.7)	12.7 (6.7–20.3)	**<0.001**
Time on ART (years), median (IQR)	19.3 (17.0–22.6)	9.7 (5.9–16.1)	**<0.001**
Current ART, n (%) - 2 NRTI + (1 NNRTI or 1 PI or 1 II) - PI-based dual therapy - PI-based monotherapy	21 (40.4) 15 (28.8) 16 (30.8)	35 (70.0) 12 (24.0) 3 (6.0)	**0.001**
Current ART including 3TC/FTC, n(%)	24 (46.2)	47 (94.0)	**<0.001**
Time on current ART (years), median (IQR)	4.5 (3.0–7.1)	3.5 (2.2–6.5)	NS
Years of HIV-RNA suppression, median (IQR)	8.8 (5.7–12.3)	6.3 (4.2–10.9)	NS

No differences regarding race, CD4 nadir, current CD4 count and CDC stage

Detection of 3TC-RM by PS and NGS according to prior history of mutations*

Historical 3TC-RM (n=48)
No historical 3TC-RM (n=45)

PS: 14 / 26,90% ; 1 / 2.0%
NGS >20%: 22 / 45,80% ; 3 / 6,7%
NGS >5%: 36 / 75,00% ; 8 / 17,8%
NGS >1%: 42 / 87,50% ; 16 / 35,5%

*PS did amplify 1 sample from one participant without historical mutations.
NSG did not amplify samples from 9 participants (4 with historical mutations)

Comparison of detection of 3TC-RM by NGS at different thresholds in participants with and without detection of mutations by PS*

3TC-RM in pvDNA by PS (n=14)
No 3TC-RM in pvDNA by PS (n=78)

NGS >20%: 11 / 78,57% ; 14 / 17,95%
NGS >5%: 14 / 100% ; 30 / 38,4%
NGS >1%: 14 / 100% ; 44 / 56,41%

* All comparisons p<0.001, except NGS>1% comparison in pvDNA p=0.002

Univariate analysis for factors associated to detection of 3TC-resistance mutation in pvDNA in those participants with historical 3TC-resistance mutations

	OR for M184V/I and/or K65R/E/N detection by PS (n=52)	OR for M184V/I and/or K65R/E/N detection by NSG>20% (n=48)	OR for M184V/I and/or K65R/E/N detection by NSG>5% (n=48)	OR for M184V/I and/or K65R/E/N detection by NSG>1% (n=48)
Male sex	0.48 (0.13–1.71)	0.43 (0.12-1.51)	0.35 (0.07–1.87)	0.40 (0.04–3.76)
Age >50 years old	1.69 (0.40–7.20)	1.41 (0.41-4.87)	0.67 (0.15–2.93)	0.40 (0.04–3.76)
HIV acquisition by IDU	1.15 (0.24–5.39)	1.6 (0.36-7.07)	**12.86 (1.29–128.14)***	-
Years since HIV infection diagnosis	1.06 (0.96–1.16)	**1.1 (0.99-1.22)****	**1.16 (1.02–1.32)***	1.06 (0.93–1.22)
Years with suppressed HIV-RNA	1.05 (0.90–1.23)	1.06 (0.92.1.23)	0.99 (0.83–1.16)	0.99 (0.80–1.23)
Years on ART	**1.14 (0.99–1.33)****	1.11 (9.97-1.27)	1.08 (0.94–1.24)	1.06 (0.89–1.26)
Years on current ART	1.15 (0.90–1.47)	1.02 (0.81-1.27)	1.01 (0.78–1.31)	0.95 (0.68–1.32)
3TC in current ART	**0.22 (0.05–0.92)***	**0.34 (0.1-1.12)****	0.51 (0.14–1.92)	0.83 (0.15–4.58)
3-drugs regimen	**0.14 (0.02–0.79)***	**0.13 (0.03-0.6)***	0.62 (0.14 – 2.73)	0.82 (0.12–5.67)

*p<0.05, **p<0.1

CONCLUSIONS

- Proviral DNA population sequencing detects a minority of historical 3TC resistance mutations. **Next generation sequencing increases sensitivity**, but the 5% threshold still misses one quarter of historical 3TC resistance mutations.

- A **regimen including 3TC is associated with no-detection** of archived 3TC resistance mutations in proviral DNA by population sequencing

P-110 Dolutegravir and Lamivudine for maintenance of HIV viral suppression in adults with and without historical resistance to lamivudine:48-week results of a pilot clinical trial (ART-PRO)

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