Effectiveness of Single- vs Multiple-Tablet Regimens as First-line ART in ICONA Cohort

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BACKGROUND:

- **Single-tablet regimens (STRs)** have been associated to **better adherence and virological control, longer persistence and reduced rates of hospitalizations compared to multi-tablet regimens (MTRs)** in meta-analysis of randomized clinical trials[1,2] and previous observational reports [4-8]. However, **most of these studies were conducted on antiretroviral (ARV) regimens which are no longer recommended**.
- Moreover, **a recent meta-analysis failed to demonstrate significant benefits of fixed dose combinations over individual drugs** in terms of virological failure, drug resistance development and discontinuation for adverse events[9].
- These findings, along with the current availability of both new and generic treatment options, prompts the need of **an updated comparison of STRs versus MTRs as first-line antiretroviral therapy (ART).**

AIM:

The aim of this study was to **evaluate and compare the effectiveness of first-line STRs versus MTRs**, after stratifying MTRs according to the number of pills/daily administrations.

STUDY DESIGN AND METHODS:

STUDY DESIGN AND POPULATION:

✓ Retrospective, observational, multicentric study including **all patients, enrolled in ICONA Foundation cohort, who started a first-line triple ART with currently recommended or alternative regimens, according to EACS Guidelines[10], from January 2011 to December 2017**.

✓ Icona is a nation-wide cohort including HIV-infected patients, naïve from ART at the enrollment, who are prospectively followed in 52 Italian centres.

✓ Exclusion criteria: ART < 30 days and less than 2 HIV-RNA determinations after ART initiation.

✓ Patients were divided in three treatment groups, according to the antiretroviral regimen started:

- **Single Tablet Regimen (STR) group:** 1 pill once daily (QD) regimen
- **Multi Tablet Regimen-1 (MTR-1) group:** 2 pills QD regimen
- **Multi Tablet Regimen-2 (MTR-2) group:** 3 pills QD or bis in die (BID) regimen

OUTCOMES:

Primary Outcome:

✓ To assess **the probability and the independent risk of virological failure (VF)** in patients starting STRs versus MTRs.

Secondary Outcomes:

✓ To assess **the independent risk of VF followed by ART switch (VF plus switch)** of STRs versus MTRs.

✓ To assess **the probability and the independent risk of virological suppression (VS)** of STRs versus MTRs.

✓ The **VF and VF plus switch outcomes** were assessed in **total population,** in the subgroup of **patients starting an INSTI-based regimen** and in the subgroup of **patients starting regimens available as both STR and MTR** (TDF, FTC, EFV and ABC, 3TC, DTG). The **VS outcome** was assessed only in the subgroup of **patients starting an INSTI-based ART.**

DEFINITIONS:

✓ **Virological Failure:** confirmed viral load (VL)>200 copies/mL, occurring 6 months after ART start.

✓ **Virological Failure plus ART switch:** a VL > 200 copies/mL occurring 6 months after ART start, followed, within 3 months, by ART switch (any drug in the regimens, TDF to TAF and PI/r to PI/c switch excluded).

✓ **Virological Suppression:** confirmed VL< 50 copies/mL.

STATISTICAL ANALYSIS:

✓ Baseline (BL) characteristics were compared among the groups using Chi-square test and non parametric tests, as appropriate.

✓ Probabilities of VF and VS (only for INSTI-subgroup) were estimated by Kaplan-Meier analysis.

✓ Cox multivariable analysis were fitted to evaluate the independent risk of VF, VF plus switch and VS for STRs versus MTRs, after adjusting for main confounding factors.

✓ In total population, VF analysis was stratified according to BL VL, due to different distribution of the regimens in the two strata.

RESULTS:

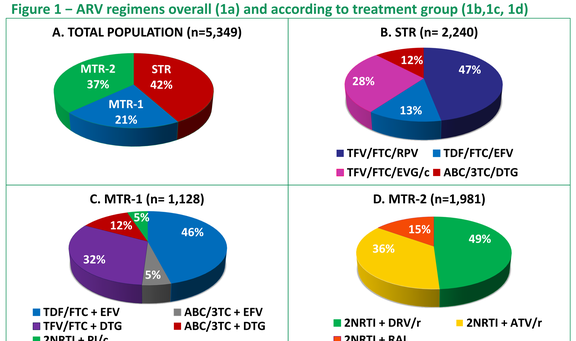
- 5349 patients were included: 42% started a STR, 21% a 2 pills QD-MTR (MTR-1) and 37% a 3-pills QD or BID-MTR (MTR-2).
- Patients starting a STR were more likely to be younger, MSM, to have a more preserved immunocompetence at BL and to have started ART more recently [Table 1].
- Regimens were based on NNRTI in 35.8%, boosted PI in 32.7% and INSTI in 31.5% patients, respectively. A detailed description of regimens according to treatment groups is reported in Fig 1.

Table 1 – Baseline Characteristics

Characteristic	STR (n=2,240)	MTR-1 (n=1,128)	MTR-2 (n=1,981)	p-value	Total (n=5349)
Female gender*	370 (16.5%)	159 (14.1%)	406 (20.5%)	**<0.001**	935 (17.5%)
Age, years**	38 (30-46)	39 (31-48)	40 (32-48)	**<0.001**	39 (31-47)
Risk Factor for HIV*				**<0.001**	
-Homosexual contacts	1217 (54.3%)	567 (50.3%)	824 (41.6%)		2608 (48.8%)
- Heterosexual contacts	730 (32.6%)	410 (36.3%)	857 (43.3%)		1997 (37.3%)
-IDU	135 (6.0%)	54 (4.8%)	155 (7.8%)		344 (6.4%)
-Other/Unknown	158 (7.0%)	97 (8.6%)	145 (7.3%)		400 (7.5%)
Non Italian born*	516 (23.0%)	245 (21.7%)	447 (22.6%)	0.689	1208 (22.6%)
AIDS diagnosis*	112 (5.0%)	117 (10.4%)	252 (12.7%)	**<0.001**	481 (9.0%)
Positive HCV serology*	141 (6.3%)	52 (4.6%)	164 (8.3%)	**<0.001**	357 (6.7%)
Median years from HIV diagnosis**	4.4 (1.4-32.8)	2.1 (0.9-15.6)	2.0 (0.7-16.6)	**<0.001**	2.7 (1.0-23.1)
BL CD4 cells count, cell/mm3**	424 (295-574)	331 (174-470)	276 (114-422)	**<0.001**	357 (190-495)
BL HIV RNA, log_{10} cp/mL**	4.45 (3.89-4.87)	4.84 (4.28-5.30)	4.95 (4.35-5.43)	**<0.001**	4.69 (4.11-5.19)
Years of cART start*				**<0.001**	
- 2011-2013	456 (20.4%)	524 (46.4%)	1118 (56.4%)		2098 (39.2%)
- 2014-2015	1040 (39.8%)	277 (24.6%)	642 (32.4%)		1904 (35.6%)
- 2016-2017	1099 (42.1%)	327 (29.0%)	221 (11.2%)		1347 (25.2%)
Type of regimen started*				**<0.001**	
- 2 NRTI + NNRTI	1335 (59.6%)	578 (51.2%)	-		1913 (35.8%)
- 2 NRTI + PI/b	-	53 (4.7%)	1696 (85.6%)		1749 (32.7%)
- 2 NRTI + INSTI	905 (40.4%)	497 (44.1%)	285 (14.4%)		1687 (31.5%)
NRTI backbone*				**<0.001**	
- Tenofovir (TFV)/FTC	2175 (97.1%)	1096 (97.1%)	1973 (99.6%)		5244 (98.0%)
- ABC/3TC	65 (2.9%)	32 (2.8%)	8 (0.4%)		105 (2.0%)

* number (%); ** median (interquartile range, IQR)

Figure 1 – ARV regimens overall (1a) and according to treatment group (1b,1c, 1d)



a. Total Population

Figure 2 – Estimated Probability of Virological Failure

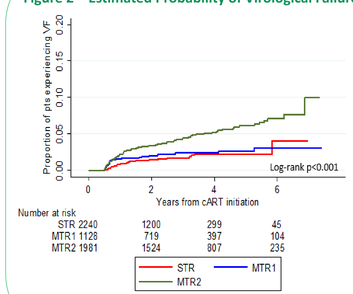
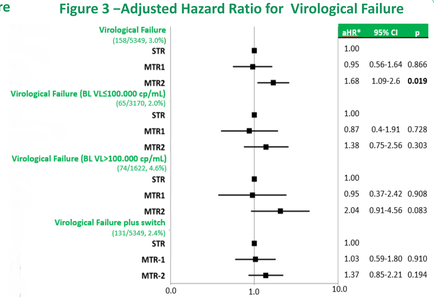


Figure 3 –Adjusted Hazard Ratio for Virological Failure



*After adjusting for gender, age, HIV risk factor, ethnicity, AIDS defining event, HCV, time from HIV diagnosis, BL HIVRNA, CD4, CD8, year of ART start, backbone, third drug (INSTI vs no INSTI), number of VL/year.

- Over a median follow-up of 2.5 years (IQR 1.4-4.1), 158/5349 (3.0%) patients experienced VF. **The probability of VF was higher for MTR-2 versus STR group (p<0.001) but comparable between MTR-1 versus STR group** (p=0.442) [Fig 2].
- By multivariate analysis, after controlling for the main confounders, **MTR-2 was associated to a higher risk of VF compared to STR** (aHR 1.68, p=0.019) whereas **no differences were found between MTR-1 and STR group** [Fig 3].
- Other predictors of VF were higher BL VL (aHR 2.17, p<0.001), non-Italian origin (aHR 2.72, p<0.001) and a previous AIDS diagnosis (aHR 1.70, p=0.018). Conversely, having started ART in 2014-2015 (aHR 0.64, p=0.035) and 2016-2017 (aHR 0.36, p=0.012) compared to 2011-2013 was associated with a lower risk of VF [data not shown].
- **A similar risk of VF among the groups was found after stratifying for BL VL**. Likewise, **no significant differences in the risk of switching ART after a single VL >200 copies/mL were observed** [Fig 3].
- **In the subgroup of patients starting an INSTI-based regimen**, **the probability of VF and VS was comparable among the groups** [Fig 4, 5]. **Similar risk of VF, VF plus switch and VS among the groups** was confirmed at multivariable analysis [Fig 6].
- Restricting the analysis to **the subgroup of patients starting regimens available as both STR and MTR, a comparable probability of VF and independent risk of VF and VF plus ART switch was found** [Fig 7, 8]

b. Patients starting INSTI-based regimens (n=1687)

Figure 4 – Estimated Probability of Virological Failure

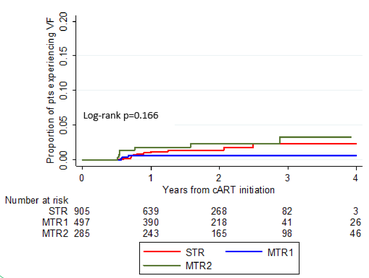


Figure 5 – Estimated probability of Virological Suppression

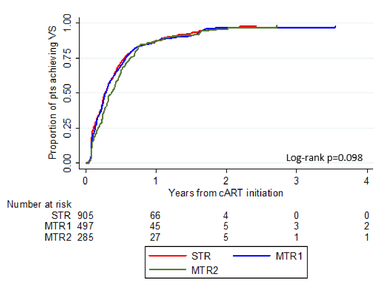
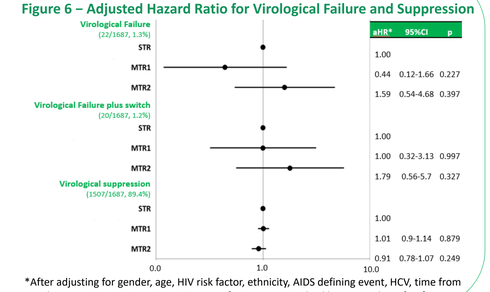


Figure 6 – Adjusted Hazard Ratio for Virological Failure and Suppression



*After adjusting for gender, age, HIV risk factor, ethnicity, AIDS defining event, HCV, time from HIV diagnosis, BL HIVRNA, CD4, CD8, year of ART start, NRTI backbone, number of VL/year.

c. Patients starting regimens available as both MTR and STR [TDF,FTC,EFV (n=802) or ABC,3TC,DTG (n=408)]

Figure 7 – Estimated Probability of Virological Failure

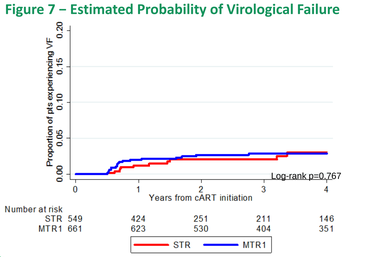
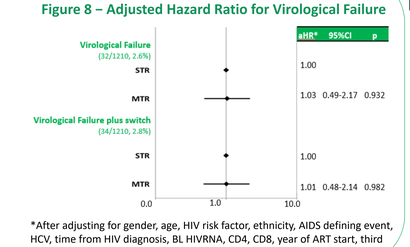


Figure 8 – Adjusted Hazard Ratio for Virological Failure



*After adjusting for gender, age, HIV risk factor, ethnicity, AIDS defining event, HCV, time from HIV diagnosis, BL HIVRNA, CD4, CD8, year of ART start, third drug (EFV vs DTG), number of VL/year.

CONCLUSIONS:

- Among currently recommended or alternative first-line antiretroviral regimens, **STRs and 2-pills QD MTRs showed a similar impact on virological failure**. Conversely, **3-pills containing MTRs were associated to a higher risk of virological failure compared to STRs**.
- In the sensitive analyses, restricted to INSTI-based first-line ART and to regimens available as both MTR and STR, **the probability of virological failure was not influenced by the number of pills/administrations.** Moreover, **in patients receiving an INSTI-based regimen, time-to-virological suppression, a possible proxy of patients' adherence, was not different by pill burden of the regimen**.
- Even though these results have the limitation of a non-randomized design, the large study population and the reproducibility across different end points and subgroups confirmed the consistency of these findings.
- These data may add important information to guide the choice of first-line ART in every-day clinical practice, particularly in the light of the current availability of generic antiretroviral drugs.

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