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## Antiretroviral therapy in geriatric HIV patients: The GEPO cohort study

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1 **Antiretroviral therapy in geriatric HIV patients: the GEPPPO cohort study**

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6 behalf of GEPPPO<sup>+</sup> (GEriatric Patients living with HIV/AIDS: a Prospective  
7 Multidimensional cOhort) Study Group.

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28 **Running title:** Treatment in aging patients.

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## 41 ABSTRACT

### 42 Background

43 GERiatricPatients living with HIV/AIDS (GEPP0) is a prospective observational multi-  
44 centric cohort including HIV infected geriatric patients. We hypothesized that the HIV  
45 infected GEPP0 cohort may help characterize ARV prescribing criteria used in real life  
46 by Italian Infectious Disease (ID) physicians.

### 47 Methods

48 Cross-sectional study describing current antiretroviral (ART) regimen in an HIV geriatric  
49 population ( $\geq 65$  years).

50 Antiretroviral strategies were categorized as follows: (i) MDR (multi-drug regimens),  
51 triple or mega combination of ART; (ii) LDR (less drug regimens), less than three ART  
52 compounds.

53 Multi-morbidity (MM) was defined as the presence of three or more non-  
54 communicable diseases, and Polypharmacy (PP) as the use of five or more medications  
55 in chronic use.

56 Four alternative combinations, ie MM+PP+, MM+PP-, MM-PP+, MM-PP-, were used in  
57 logistic regression analyses.

### 58 Results

59 A total of 1222 HIV positive patients were included – median age 70 years. Females  
60 amounted to 16% of the cohort. Median duration of HIV was 17 years, while 335

61 population members were infected for longer than 20 years. MM was present in 64%  
62 and PP in 37% of the patients.

63 ARV prescription consisted of triple therapy in 66.4%, dual therapy in 25.3%,  
64 monotherapy in 6.5% and “mega-ART” with more than three drugs in 1.64% of the  
65 patients.

66 In multivariate logistic regression MM and PP were predictive for mono-dual, NRTI-  
67 sparing and TDF-sparing combinations. Female gender and age were predictors of  
68 boosted free ARV regimens

## 69 **Conclusions**

70 High prevalence of non-conventional ARV regimens in elderly HIV patients suggests  
71 clinicians’ effort to tailor ARV regimens according to age, HIV duration, MM and PP.

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82 **TEXT**

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84 **Background**

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86 Antiretroviral therapy has been one of the most important goals of contemporary  
87 medicine, credited as it is with enabling people to grow old with HIV.

88 Standard antiretroviral therapy (ART) consists of the combination of a minimum of  
89 three different antiretroviral (ARV) drugs. These underlie the so called **Multi-Drug**  
90 **Regimens (MDRs)**, preferably from at least two different classes, to maximally suppress  
91 the HIV virus and stop the progression of HIV disease. Currently, there are six classes of  
92 antiretroviral agents available: nucleoside (or nucleotides) reverse transcriptase  
93 inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease  
94 inhibitors (PIs), fusion inhibitors (FI), entry inhibitors (EIs) and integrase inhibitors  
95 (INSTIs).

96 Based on evidence from clinical trials and expert opinion, current international  
97 treatment guidelines have established preferred recommended regimens that include  
98 2 NRTIs + 1 INSTI, 2 NRTIs + 1 NNRTI or 2 NRTIs + 1 PI.<sup>1-3</sup> However, all agree that ART  
99 must be tailored according to patient clinical condition and preferences.

100 The pillars of the choice of ART in both naïve and experienced patients are ARV  
101 potency and resistance, ARV impact on comorbidity, the risk for drug-drug interaction,  
102 costs, tolerability and convenience in fixed-dose combination (single tablet regimens –  
103 STR, in particular).

104 The tailored approach to ART produced an increasing number of “non conventional”  
105 ARV regimens either in dual regimens (1 NRTI + 1IP or 1 INSTI + 1IP) or monotherapy  
106 (1PI/r-**lopinavir/r or darunavir/r**) – the so called **Less Drug Regimens (LDR)** – as an  
107 alternative option.

108 In recent years, some guidelines have solicited the tailoring principle for the  
109 management of the elderly HIV-infected population. What all agree on is the need for  
110 an intensive screening for co-morbidities by reason of the association of these clinical  
111 conditions with advanced age. Still, only a few (CDC and Italian Society of Infectious  
112 and Tropical Diseases)<sup>3</sup> attempt preferred options, but they identify areas of  
113 uncertainty in the use of ARV in elderly HIV patients.

114 In particular, older HIV-infected patients may suffer from age-related co-morbidities, in  
115 particular kidney, bone and heart disease that challenge ARV toxicities. From this  
116 perspective, an increasing number of LDR has been used, albeit supported by limited  
117 data from randomised clinical studies, in order to build regimens sparing tenofovir,  
118 abacavir, NRTI or boosted combinations.

119 Comorbidities frequently aggregate in complex multi-morbidity pictures (MM), which  
120 implies the need for polypharmacy with potential high risk for drug-drug interaction  
121 (DDI)<sup>4,5</sup>. From this perspective, ARV classes with less impact for DDI are increasingly  
122 used, INSTI in particular, parallel to the reduction of boosted regimens, PI/r in  
123 particular. Ritonavir and cobicistat are “boosters” known to inhibit CYP3A4 and 2D6<sup>6,7</sup>  
124 cytochrome pathway, metabolizing nearly 70% of all medications undergoing CYP450  
125 metabolism<sup>8,9</sup>. PIs and NNRTIs can also decrease the activity of P-glycoprotein, a

126 ubiquitous transport protein<sup>10</sup> which plays a significant role in drug absorption and  
127 disposition<sup>11</sup>.

128 Finally, ARV prescribers should also consider age-associated physiological changes  
129 altering pharmacokinetics (ie, decreased GI transit, increased fat-to-lean body ratio,  
130 reduced hepatic metabolism and renal elimination)<sup>12</sup> and pharmacodynamics (ie,  
131 physiological and biochemical effects of drugs on the body), resulting in increased  
132 sensitivity to medications and higher risk for adverse side effects.

133 GERiatricPatients living with HIV/AIDS (GEPP0) is a prospective observational multi-  
134 centric cohort including consecutive HIV-infected geriatric patients in care in 10 HIV  
135 Clinics in Italy compared to HIV-negative individuals. It aims to describe health status  
136 and transition over time in HIV-infected patients above 65 years.

137 We hypothesized that the HIV+ GEPP0 cohort may help to take of characterizing ARV  
138 prescribing criteria used in real life by Italian Infectious Disease (ID) physicians.

139 The present analysis of the GEPP0 cohort aims to describe the current use of ART in a  
140 well characterized HIV geriatric population.

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### 143 **Methods**

144 This is a cross-sectional study describing the current ART regimen in an HIV geriatric  
145 population ( $\geq 65$  years), at the time of cohort entry. We choose this age according to  
146 geriatric literature. The initial visit was performed between June 2015 and May 2016.



147 The inclusion criteria were as follows: age  $\geq$  65 years, HIV Antibodies positive, being on  
148 highly active antiretroviral therapy (HAART) for at least 6 months and a signed informed  
149 consent. These patients were recruited in 10 HIV clinics in Italy.

150 Demographic and clinical characteristics, such as current and nadir CD4 cell counts,  
151 ratio CD4/CD8, plasma HIV RNA, duration of HIV, presence of co-infection with  
152 hepatotropic virus, current ART regimen and concomitant therapeutic drugs were  
153 recorded.

154 Duration of HIV infection was calculated as the time between HIV diagnosis and the  
155 last visit. This variable was stratified into  $< 10$ ,  $10 - 20$  and  $>20$  years of duration. The  
156 choice of these time periods did not only parallel the tertile distribution of the last  
157 variable. It also identified the subset of individuals aging with HIV since pre-HAART,  
158 early and late-HAART periods.

159 Comorbidity diagnoses were based on criteria previously used in our studies[16]. The  
160 category of CVD included the following diagnoses: myocardial infarction, coronary  
161 artery disease, peripheral vascular disease, stroke, angina pectoris, coronary artery  
162 bypass grafting, and angioplasty. Hypertension (HTN) was defined as blood pressure  
163  $>140/90$  mmHg over two consecutive measurements, type 2 diabetes mellitus (T2DM)  
164 as fasting serum glucose levels  $> 126$  mg/dL, and chronic kidney disease (CKD) as eGFR  
165 (glomerular filtration rate)  $< 60$  mL/min using the Modification of Diet in Renal Disease  
166 (MDRD) estimating equation. Hypertension and T2DM diagnoses were also identified  
167 through current use of antihypertensive and antidiabetic drugs, respectively.  
168 Dyslipidaemia was diagnosed in patients with fasting total cholesterol  $> 200$  mg/dL or

169 triglycerides > 150 mg/dL, or current use of statins. **Chronic Obstructive Pulmonary**  
170 **Disease (COPD)** was defined with pulmonary function testing (spirometry, diffusion  
171 capacity of carbon monoxide [DLCO], demonstrating **forced expiratory volume**  
172 **(FEV1)/forced vital capacity (FVC) ratios < 70%**. Multi-morbidity (**MM**) was defined as  
173 the presence of three or more non-communicable diseases.

174 Polypharmacy (**PP**) was defined as the use of five or more medications in chronic use,  
175 **excluding ARV medications**. To distinguish acute exposure to a drug from chronic use  
176 of medication, the latter was classified as the use for at least four consecutive months.

177 Antiretroviral strategies were categorized as follows (i) **MDR**, triple or mega  
178 combination of ART; and (ii) **LDR**, less than three ART compounds administered as  
179 either monotherapy or dual combination therapy.

## 180 **Statistical analysis**

181 Comparisons between the groups (MDR and LDR) were performed using  $\chi^2$  test for  
182 categorical variables and T-test or Mann-Whitney U-test for normally and non-  
183 normally distributed continuous variables, respectively.

184 Results were expressed as mean (SD) or median (IQR) for normal and non-normal  
185 continuous distributed variables, or frequency (%) for categorical variables. Separate  
186 multivariate logistic regression was built to identify predictors of “non-conventional”  
187 ARV strategies, including TDF-sparing, un-boosted, NRTI-sparing and mono/dual  
188 therapies.

189 Logistic regression was used as the following clinically meaningful variables co-vary:  
190 age (per one-year increment), gender (female as reference), HIV duration (<10 years as  
191 reference), MM and PP. By virtue of the potential overlap between MM and PP, we  
192 built a joint dummy variable, using MM negative PP negative (MM-PP-) as reference  
193 and three alternative combinations, ie MM+PP+, MM+PP-, MM-PP+.

194 Statistical analyses were performed using the “R” Software, version 3.2.

## 195 **Ethics**

196 An institutional review board (IRB) approval was obtained from the Research Ethics  
197 Board of each individual centre belonging to the GEPPPO cohort (Protocol number 1710,  
198 Reference 39/16, Servizio Sanitario Regionale Emilia Romagna, Azienda Ospedaliero  
199 Universitaria di Modena). All participants provided written consent at their initial in-  
200 clinic visit.

## 201 **Results**

202 A total of 1222 HIV positive patients were included. Table 1 describes demographic  
203 and clinical characteristic of the HIV infected population in the GEPPPO cohort,  
204 comparing the ART regimen groups (MDR and LDR).

205 HIV patients undergoing LDR appear to have acquired HIV infection at an earlier age,  
206 and they have been living with HIV for a longer period of time. The comorbidity burden  
207 is higher in this patient group, which displays a higher prevalence of MM and PP.  
208 MM+PP+ correlate with LDR prescription.

209 The ARV prescriptions of GEPPPO participants were triple therapy in 66.4%, dual  
210 therapy in 25.3%%, mono therapy in 6.5% and a “mega-ART” with more than three  
211 drugs in 1.64% of the patients (Figure 1).

212 Figure 2 sorts mono/dual or triple/mega strategies according to HIV duration –  
213 stratified into <10, 10-20 and >20 years of HIV exposure (Panel a) – and by the four  
214 possible combination of MM and PP (MM-PP-, MM+PP-, MM-PP+ and MM+PP+) (Panel  
215 b).

216 A univariate analysis of HIV duration appears to drive mono/dual therapy but not  
217 triple/mega therapy.

218 Figure 3 shows the top 10 prescribed ARV combinations and drug classes in MDR and  
219 LDR regimens. Both MDR and LDR regimens show a highly disperse number of ARV  
220 combinations. In mono/dual therapy for 384 patients, there were 68 different ARV  
221 regimens, while in the triple/mega group 113 ARV regimens were recorded for 839  
222 patients. The most commonly prescribed third agent in MDR was NNRTI (44.82%). LDR  
223 regimen was an INSTI dual regimen in 40.62% of the cases.

224 Figure 4 shows the multivariate logistic regression for the use of non-conventional ARV  
225 strategies. MM and PP were predictive for mono-dual, NRTI-sparing and TDF-sparing  
226 combinations. Female gender and age were predictors of boosted free ARV regimens.

## 227 **Discussion**

228 The GEPPPO cohort is one of the largest existing geriatric cohorts in HIV. It depicts a well  
229 characterized population of people aging with HIV, with a median duration of HIV of 17

230 years and a homogeneous exposure to decades of HIV infection: <10 years, 10 – 20  
231 years and above 20 years. Virological control is similar in patients treated with MDR o  
232 LDR, highlighting that in this population tailored antiretroviral therapy is efficacious.

233 By reason of female predominance in gender distribution of the general geriatric  
234 population, the GEPPPO cohort is over representative of male patients in relation to the  
235 HIV epidemic in Italy, mainly represented by MSM in this cohort (data not shown). This  
236 population is doing remarkably well with regard to immune-virological control of HIV.  
237 The WHO objective of 90% of HIV infected people with undetectable HIV viral load is  
238 fully reached (94%). Current median CD4 is above 600/ $\mu$ L and CD4/CD8 higher than  
239 0.9. Prevalence of HBV co-infection (10%) is higher than in the general population and  
240 even higher than in the HIV population of a younger age. This may be correlated with  
241 the fact that HBV vaccination was introduced in Italy as a public health policy in 1991:  
242 by that time, people belonging to this cohort were above the age of 40, and  
243 presumably most of them were already HBV infected. As expected, this population  
244 suffers from many comorbidities, most of the time aggregating in a complex picture  
245 called multi-morbidity. The 64% prevalence of MM turns this condition into the norm  
246 in this cohort, and it drives the high prevalence of PP (37%). In this study, we chose a  
247 restrictive definition of PP (without taking note of the burden of ARV in the count of  
248 the chemical products prescribed to in the same individual at the same time) to avoid  
249 saturation of the prevalence of this condition in the study sample.

250 The choice to divide the study population into MDR and LDR ARV prescription  
251 strategies was driven by the observation that one third of the cohort (32%) was

252 exposed to unconventional LDR regimens, either mono (7%) or dual (25%) regimens.  
253 These regimens were more frequently NRTI-sparing (57%) and TDF-sparing (67%), but  
254 less likely boosted free (34%).

255 We hypothesized that the GEPP0 cohort may help characterize ARV prescribing  
256 criteria. However, it must be acknowledged that many of the driving forces which rule  
257 ARV prescription in real life cannot be reconstructed retrospectively. In that regard,  
258 the major limitation of this study is inherent in its multicentre observational nature  
259 unable to check for resistance patterns, tolerability, cost, patient convenience or even  
260 calendar year. As a matter of fact, when a new ARV agent is introduced, this is not  
261 always immediately available to all centers across Italy. Nevertheless, we focused on  
262 two major ARV prescription drivers which are of paramount importance in geriatric  
263 cohorts, MM and PP.

264 In the GEPP0 cohort, MM was a combination of highly prevalent comorbidity  
265 conditions including dyslipidaemia (71%), HTN (63%), CVD (20%) and CKD (19%). DEXA  
266 (dual-energy x-ray absorptiometry) data were available in a subset only of the cohort  
267 (157 participants). In these patients, low bone mass (lumbar t-score <-2) was present  
268 in 26% of the cases (data not shown). These comorbidities may impact on the use of  
269 boosted regimens frequently associated with dyslipidaemia<sup>13,14</sup>, abacavir being  
270 presumably associated with an increased risk of CVD<sup>15,16</sup> and TDF definitively  
271 associated with kidney impairment and fracture risk<sup>17-19</sup>.

272 Polypharmacy is a well-recognised public health concern but has been poorly studied  
273 in HIV infection.

274 Polypharmacy in the older population might raise several concerns related to an  
275 increased risk of drug-drug and drug-disease interactions, poor adherence to  
276 treatment, and increased risk of adverse drug reactions<sup>20,21</sup>.

277 Boosted regimen does increase the risk for DDI. Therefore, several guidelines  
278 recommend avoiding boosted ARV regimen in case of polypharmacy.<sup>22,23</sup>

279 In addition, medications often used to treat chronic and acute diseases are rarely  
280 tested in the older population.<sup>24</sup> In the oldest old population, this is further  
281 complicated by the high prevalence of geriatric conditions (ie, cognitive impairment,  
282 functional deficits and geriatric syndromes). These can impact on treatment adherence  
283 and limit life expectancy, which can further reduce the beneficial effect of prescribed  
284 medications.<sup>25-27</sup>

285 The strong association between PP and MM represents a methodological challenge to  
286 separately evaluating the associations between PP and clinical harm. As expected, in  
287 the GEPO cohort comorbidities implied the need for specific pharmacological  
288 interventions for treatment or prevention (MM+PP+ = 33%). Interestingly,  
289 nonetheless, there was a similar proportion of patients with MM who did not have PP  
290 (MM+PP- = 30%). A quite worrying subset of people with PP did not have MM (MM-  
291 PP+ = 6%) and merit further clinical attention.

292 The classification into LDR and MDR very clearly stratified the cohort into two different  
293 populations. The former is significantly exposed to HIV infection for a longer time,  
294 acquired HIV at a younger age, and has a higher prevalence of MM and PP. Apparently,

295 clinicians' choice of LDR in this population whiteness the recognition of the higher  
296 vulnerability of this subgroup of people.

297 One of the most **surprising** findings in the GEPP0 cohort is the impressive number of  
298 different ARV drugs and drug classes, respectively 72 and 17 in the 390 patients  
299 undergoing LDR, and 110 and 34 for the 839 patients undergoing MTR. In the latter  
300 group, the following "third agent" class may be recognized: NNRTI 49%, PI/r 26% and  
301 INSTI 25%.

302 In the LDR group, NNRTI is present in 23%, PI/r in 58 % and INSTI in 42%. The latter are  
303 mainly associated with PI/r 15% or NNRTI 14% or 3TC 7%.

304 Unfortunately, there is very little high-quality evidence to guide ARV prescriptions for  
305 the elderly HIV population, particularly those with MM,<sup>4,5</sup> because these patients are  
306 generally excluded from clinical trials.<sup>24,28-31</sup>

307 At multivariate logistic regression, people with MM and PP more than doubled the  
308 likelihood for mono-dual regimen (OR=2.45, 95% CI: 1.45-4.21) and for a TDF-sparing  
309 regimen (OR=2.51, 95% CI: 1.5-4.28). These two groups of people almost overlap and  
310 TDF tenofovir diproxil fumarate appears to be the main driver for these dual regimens.

311 People exposed to HIV for more than 10 years had a higher probability for NRTI-  
312 sparing regimens. In this subgroup, the duration of HIV exposure may be a proxy for  
313 comorbidities, but these individuals are more likely to have an issue related to NRTI  
314 resistance, mainly generated in the pre and early HAART era.



315 Age was the only identified independent risk factor for boosted-free regimen.  
316 Clinicians may in fact be worried of the pharmacy-dynamic behavior of drugs in ageing  
317 metabolism.

318 Our data lead us to argue strongly for a tailored approach to drug treatment in HIV-  
319 positive patients with MM. Studies addressing ARV efficacy in elderly people with end-  
320 stage organ function represent innovative drug “stress tests”; in fact, these are the  
321 most informative studies at the bedside on the switch from TDF fumarate to TDF  
322 alfenamide (TAF), a recommendation for all geriatric patients due to a lower impact  
323 on bone or kidney toxicity.<sup>27</sup> TAF also has the potential to reduce both LDR and MDR  
324 regimens, decreasing the burden of ARV prescription variability not supported by  
325 randomised clinical trials. In spite of that, LDR may well continue to exist. Indeed,  
326 recent research into the superiority efficacy of PI/r+3TC as opposed to standard  
327 PI/r+2NRTIs<sup>32</sup> and the on-going trials on DTG+3TC (Gemini 1 and PADDLE trials) may  
328 definitively leave the room for LDR maintenance strategies. In SWORD trial viral  
329 suppression with a two drug regimen combining an integrase inhibitor (dolutegravir) and a  
330 non-nucleoside reverse transcriptase inhibitor (rilpivirine) in patients with HIV who have  
331 already achieved viral suppression with a three drug regimen was demonstrated,<sup>33</sup>  
332 otherwise, more adverse events were reported and led to withdrawal from the study in the  
333 dolutegravir and rilpivirine arm compared to the current antiretroviral therapy arm. This  
334 strategy could be studied in aged population, who usually need high genetic barrier to  
335 achieve continuing virological suppression.

336 ARV tailoring may also consider PP interventions.

337 Although ‘de-prescribing’ is relatively new to HIV medicine, the use of tools such as the  
338 Beers criteria,<sup>34</sup> IPET(Improving Prescribing in the Elderly Tool)<sup>35</sup> and STOPP-START

339 criteria<sup>36,37</sup> to tailor therapy and reduce harmful PP are well-established in gerontology  
340 practice, and should be extended to the HIV field.<sup>38</sup>  
341 Italian data on dual therapies based on boosted PI are available in some clinical  
342 settings and these strategies are used in 6,7-12,8% of patients.<sup>39</sup>

### 343 **Conclusions**

344 In conclusion, we have described ARV use in a large well characterised geriatric cohort.  
345 The present scenario outlines the clinicians' effort to tailor ARV regimens according to  
346 age, duration of HIV and, in particular, MM and PP. The advent of TAF and un-boosted  
347 regimens, mainly in the INSTI class, holds the potential to change this scenario rapidly,  
348 while at the same time calling for randomised clinical trials specifically addressing  
349 geriatric HIV patients.

350

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### 355 **Conflict of Interest**

356

357 SN received travel grants and speaker's honoraria from Gilead, Viiv, Janssen-Cilag and  
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367

368 **Transparency declaration.**

369

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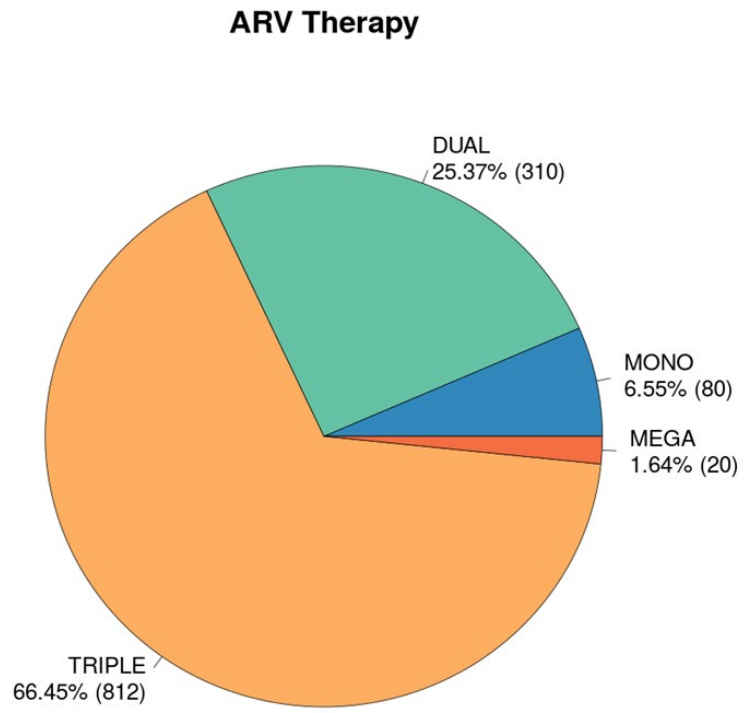
511 **Table 1:** Demographic and clinical characteristics of the population.

	<b>Total (n=1222)</b>	<b>LDR (n=390, 31.91%)</b>	<b>MDR (n=832, 68.09%)</b>	
<b>Variable</b>	Mean (SD)			p-value
<b>Sex (F)</b>	205 (16.3%)	59 (15.13%)	138 (16.59%)	0.57
<b>Age</b>	70 (68-74)	71.28 (4.22)	71.12 (4.01)	0.78
<b>HBV co-infection</b>	103 (9.83%)	33 (10.58%)	68 (9.58%)	0.7
<b>HCV co-infection</b>	141 (12.57%)	45 (13.35%)	91 (11.99%)	0.66
<b>Age at HIV diagnosis</b>	54.03 (8.83)	52.7 (9.02)	54.51 (8.6)	<0.01
<b>HIV duration (years)</b>	17.17 (7.65)	18.55 (7.83)	16.62 (7.45)	<0.01
<b>&lt;10 years</b>	263 (21.23%)	71 (18.39%)	182 (22.11%)	<0.01
<b>10-20 years</b>	561 (45.28%)	154 (39.9%)	247 (30.01%)	

>20 years	415 (33.49%)	161 (41.71%)	247 (30.01%)	
<b>CD4 Nadir</b>	197.5 (84-310)	214 (101-308.5)	190 (78-307)	0.12
<b>Current CD4</b>	644.58 (289.04)	655.59 (290.82)	638.06 (287.59)	0.45
<b>CD4 / CD8</b>	0.97 (1.45)	1.09 (2.46)	0.92 (0.55)	0.75
<b>Viral Load ≤ 40</b>	1044 (94.31%)	332 (95.13%)	692 (94.54%)	0.79
<b>Viral Load Undetectable</b>	925 (86.53%)	264 (84.62%)	647 (88.03%)	0.16
<b>Dyslipidaemia</b>	618 (71.12%)	205 (76.49%)	404 (69.06%)	0.03
<b>T2DM</b>	241 (28.45%)	91 (34.47%)	144 (25.4%)	0.01
<b>HTN</b>	551 (63.55%)	186 (69.14%)	353 (60.86%)	0.02
<b>CVD</b>	164 (19.83%)	72 (28.24%)	89 (15.98%)	<0.01
<b>CKD</b>	171 (19.21%)	76 (27.24%)	92 (15.51%)	<0.01
<b>COPD</b>	60 (7.37%)	29 (11.69%)	31 (5.63%)	<0.01
<b>MM</b>	510 (64.31%)	124 (61.08%)	212 (43.8%)	<0.01
<b>PP</b>	242 (37.29%)	97 (42.73%)	138 (33.91%)	0.03
<b>MM-PP-</b>	138 (30.32%)	32 (20.78%)	106 (35.22%)	<0.01
<b>MM+PP-</b>	138 (30.32%)	49 (31.82%)	89 (29.57%)	
<b>MM-PP+</b>	28 (6.1%)	8 (5.19)	20 (6.64%)	
<b>MM+PP+</b>	151 (33.18%)	65 (42.21%)	86 (28.57%)	
<b>NRTI-Sparing</b>	702 (57.4%)	291 (74.62%)	410 (49.28%)	<0.01
<b>TDF- Sparing</b>	842 (66.9%)	369 (94.6%)	437 (52.5%)	<0.01
<b>INSTI-use</b>	<b>357 (28.3%)</b>	<b>162 (41.5%)</b>	<b>195 (23.4%)</b>	<b>&lt;0.01</b>
<b>Boosted free</b>	623 (54.5%)	107 (34.5%)	516 (62%)	<0.01

513 **Figure1:** ARV prescription strategies.

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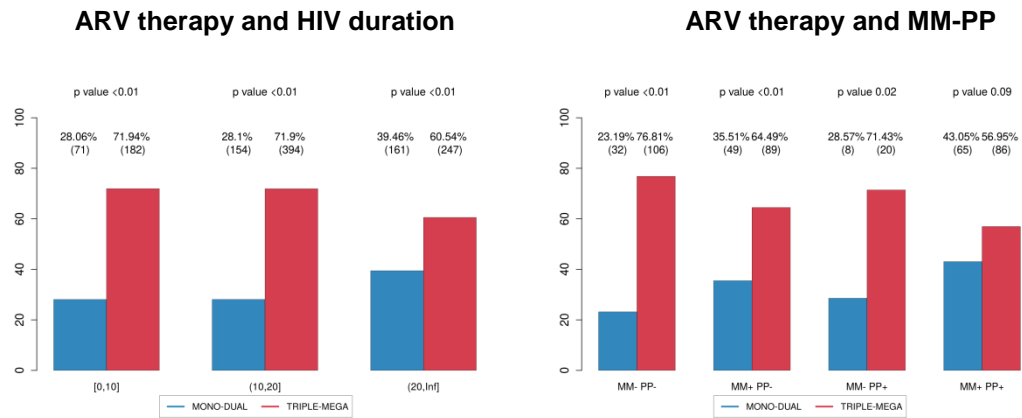
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516 **Figure 2: ARV prescription strategies according to: panel (a) duration of HIV infection**  
 517 **(categorized in three intervals: < 10, 10 - 20 and > 20 years); panel (b) association**  
 518 **between MM and PP**

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523 (a)

(b)

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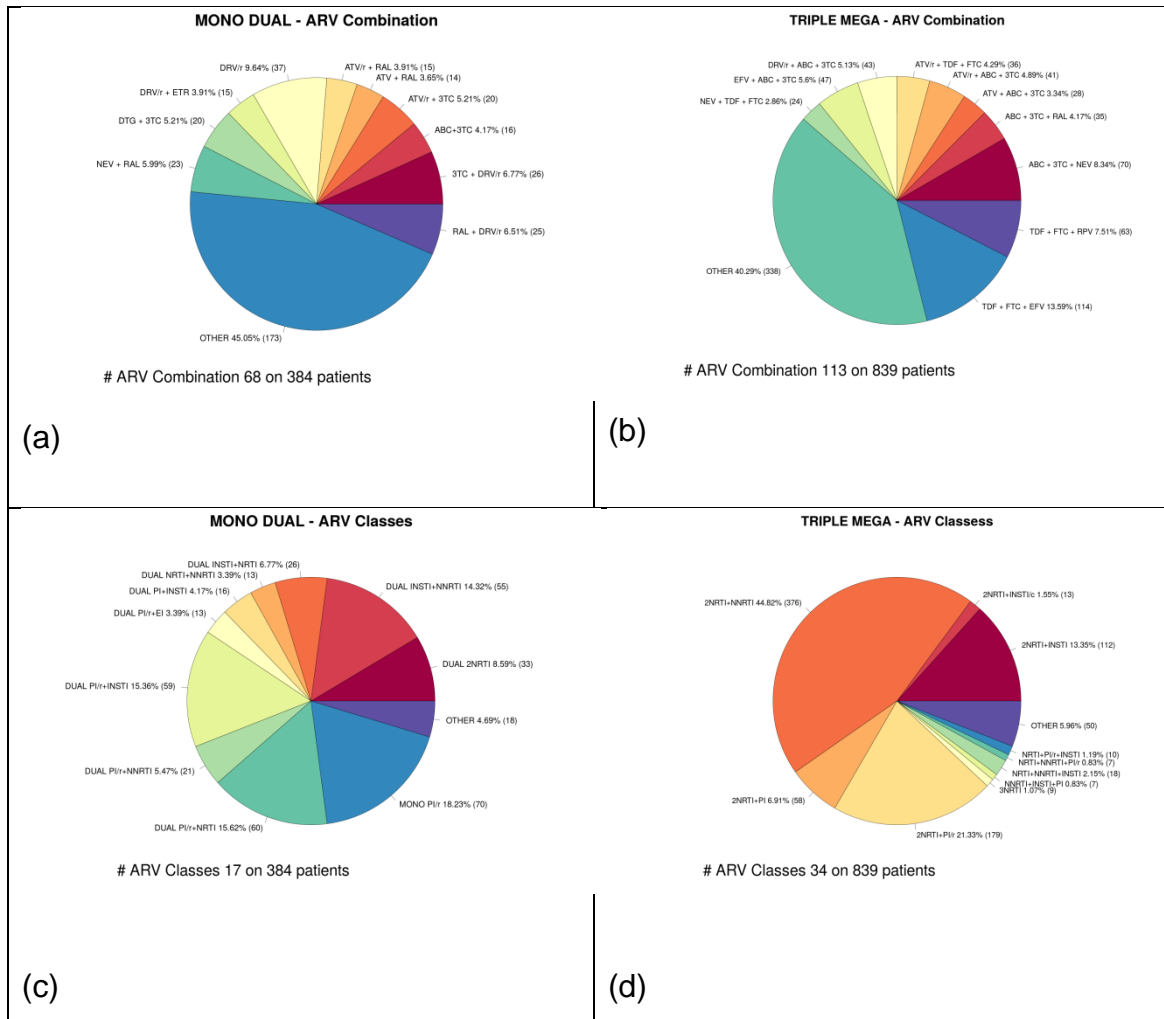
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534 **Figure 3: Top 10 prescribed ARV in MDR and LDR**

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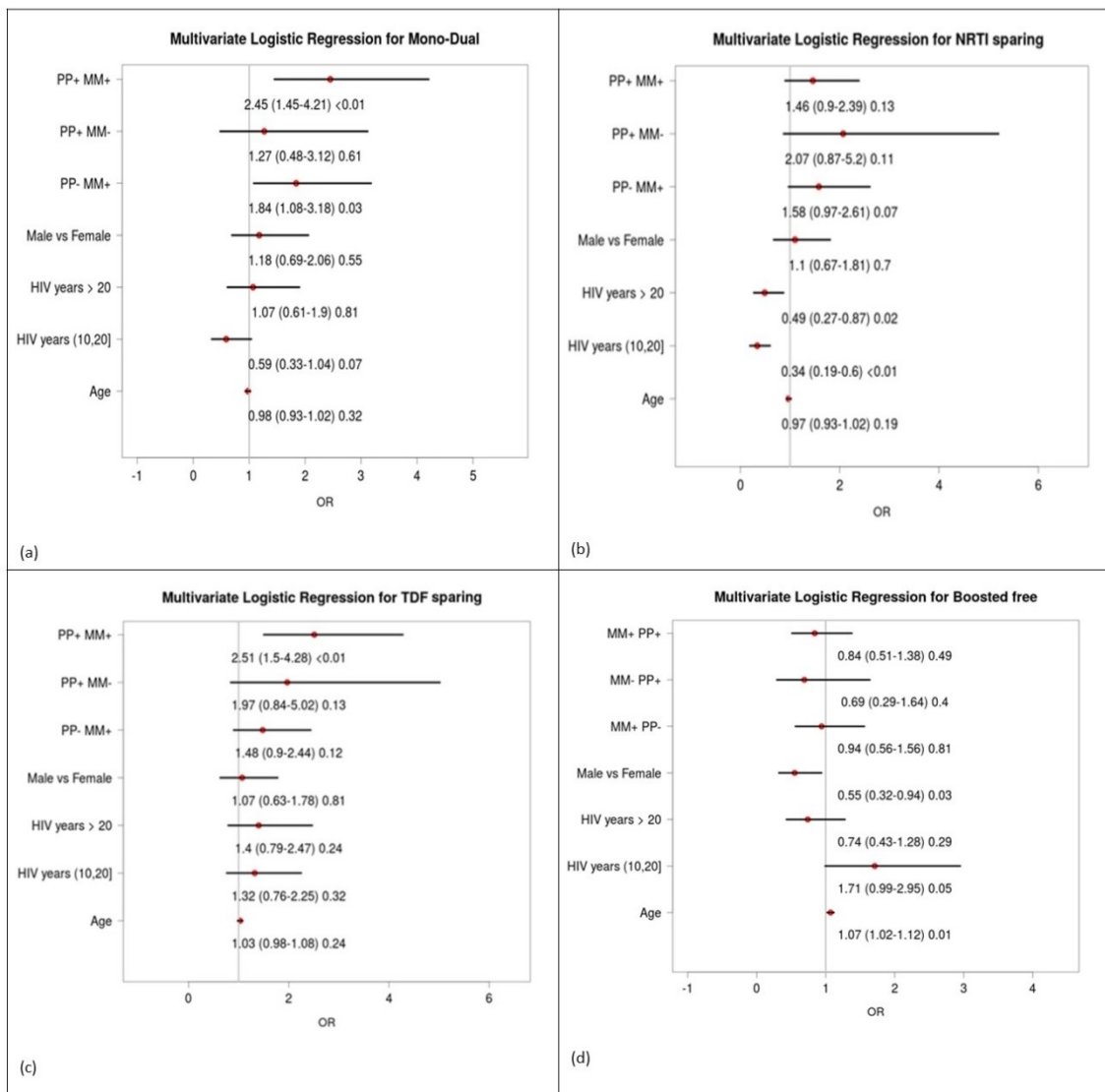
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542 **Figure 4:** Multivariate logistic regression for the use of non-conventional ARV  
543 strategies: (panel a) mono and dual combination of therapy; (panel b) NRTI-sparing  
544 therapy; (panel c) TDF-sparing regimen; (panel d) boosted-free therapy.



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