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Antiretroviral therapy in geriatric HIV patients: the GEPPo cohort study

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

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ABSTRACT

Background

GEriatricPatients living with HIV/AIDS (GEPO) is a prospective observational multicentric cohort including HIV infected geriatric patients. We hypothesized that the HIV infected GEPO cohort may help characterize ARV prescribing criteria used in real life by Italian Infectious Disease (ID) physicians.

Methods

Cross-sectional study describing current antiretroviral (ART) regimen in an HIV geriatric population (≥ 65 years).

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

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

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

Results

A total of 1222 HIV positive patients were included – median age 70 years. Females amounted to 16% of the cohort. Median duration of HIV was 17 years, while 335
population members were infected for longer than 20 years. MM was present in 64% and PP in 37% of the patients.

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

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

Conclusions

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

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

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

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

The pillars of the choice of ART in both naïve and experienced patients are ARV potency and resistance, ARV impact on comorbidity, the risk for drug-drug interaction, costs, tolerability and convenience in fixed-dose combination (single tablet regimens – STR, in particular).
The tailored approach to ART produced an increasing number of “non conventional” ARV regimens either in dual regimens (1 NRTI + 1 IP or 1 INSTI + 1 IP) or monotherapy (1 PI/r-lopinavir/r or darunavir/r) — the so called Less Drug Regimens (LDR) — as an alternative option.

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

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

Comorbidities frequently aggregate in complex multi-morbidity pictures (MM), which implies the need for polypharmacy with potential high risk for drug-drug interaction (DDI). From this perspective, ARV classes with less impact for DDI are increasingly used, INSTI in particular, parallel to the reduction of boosted regimens, PI/r in particular. Ritonavir and cobicistat are “boosters” known to inhibit CYP3A4 and 2D6 cytochrome pathway, metabolizing nearly 70% of all medications undergoing CYP450 metabolism. PIs and NNRTIs can also decrease the activity of P-glycoprotein, a
ubiquitous transport protein\textsuperscript{10} which plays a significant role in drug absorption and disposition\textsuperscript{11}.

Finally, ARV prescribers should also consider age-associated physiological changes altering pharmacokinetics (ie, decreased GI transit, increased fat-to-lean body ratio, reduced hepatic metabolism and renal elimination\textsuperscript{12} and pharmacodynamics (ie, physiological and biochemical effects of drugs on the body), resulting in increased sensitivity to medications and higher risk for adverse side effects.

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

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

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

\textbf{Methods}

This is a cross-sectional study describing the current ART regimen in an HIV geriatric population (≥65 years), at the time of cohort entry. We choose this age according to geriatric literature. The initial visit was performed between June 2015 and May 2016.
The inclusion criteria were as follows: age $\geq 65$ years, HIV Antibodies positive, being on high active antiretroviral therapy (HAART) for at least 6 months and a signed informed consent. These patients were recruited in 10 HIV clinics in Italy.

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

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

Comorbidity diagnoses were based on criteria previously used in our studies[16]. The category of CVD included the following diagnoses: myocardial infarction, coronary artery disease, peripheral vascular disease, stroke, angina pectoris, coronary artery bypass grafting, and angioplasty. Hypertension (HTN) was defined as blood pressure $>140/90$ mmHg over two consecutive measurements, type 2 diabetes mellitus (T2DM) as fasting serum glucose levels $> 126$ mg/dL, and chronic kidney disease (CKD) as eGFR (glomerular filtration rate) $< 60$ mL/min using the Modification of Diet in Renal Disease (MDRD) estimating equation. Hypertension and T2DM diagnoses were also identified through current use of antihypertensive and antidiabetic drugs, respectively. Dyslipidaemia was diagnosed in patients with fasting total cholesterol $> 200$ mg/dL or
triglycerides > 150 mg/dL, or current use of statins. Chronic Obstructive Pulmonary Disease (COPD) was defined with pulmonary function testing (spirometry, diffusion capacity of carbon monoxide [DLCO], demonstrating forced expiratory volume (FEV1)/forced vital capacity (FVC) ratios < 70%. Multi-morbidity (MM) was defined as the presence of three or more non-communicable diseases.

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

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

Statistical analysis

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

Results were expressed as mean (SD) or median (IQR) for normal and non-normal continuous distributed variables, or frequency (%) for categorical variables. Separate multivariate logistic regression was built to identify predictors of “non-conventional” ARV strategies, including TDF-sparing, un-boosted, NRTI-sparing and mono/dual therapies.
Logistic regression was used as the following clinically meaningful variables co-vary:
age (per one-year increment), gender (female as reference), HIV duration (<10 years as reference), MM and PP. By virtue of the potential overlap between MM and PP, we built a joint dummy variable, using MM negative PP negative (MM-PP-) as reference and three alternative combinations, ie MM+PP+, MM+PP-, MM-PP+.

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

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

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

HIV patients undergoing LDR appear to have acquired HIV infection at an earlier age, and they have been living with HIV for a longer period of time. The comorbidity burden is higher in this patient group, which displays a higher prevalence of MM and PP. MM+PP+ correlate with LDR prescription.
The ARV prescriptions of GEPPO participants were triple therapy in 66.4%, dual therapy in 25.3%, mono therapy in 6.5% and a “mega-ART” with more than three drugs in 1.64% of the patients (Figure 1).

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

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

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

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

Discussion

The GEPPO cohort is one of the largest existing geriatric cohorts in HIV. It depicts a well characterized population of people aging with HIV, with a median duration of HIV of 17
years and a homogeneous exposure to decades of HIV infection: <10 years, 10 – 20 years and above 20 years. Virological control is similar in patients treated with MDR o LDR, highlighting that in this population tailored antiretroviral therapy is efficacious.

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

The choice to divide the study population into MDR and LDR ARV prescription strategies was driven by the observation that one third of the cohort (32%) was
exposed to unconventional LDR regimens, either mono (7%) or dual (25%) regimens. These regimens were more frequently NRTI-sparing (57%) and TDF-sparing (67%), but less likely boosted free (34%).

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

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

Polypharmacy is a well-recognised public health concern but has been poorly studied in HIV infection.
Polypharmacy in the older population might raise several concerns related to an increased risk of drug-drug and drug-disease interactions, poor adherence to treatment, and increased risk of adverse drug reactions\textsuperscript{20,21}.

Boosted regimen does increase the risk for DDI. Therefore, several guidelines recommend avoiding boosted ARV regimen in case of polypharmacy.\textsuperscript{22,23}

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

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

The classification into LDR and MDR very clearly stratified the cohort into two different populations. The former is significantly exposed to HIV infection for a longer time, acquired HIV at a younger age, and has a higher prevalence of MM and PP. Apparently,
clinicians’ choice of LDR in this population whiteness the recognition of the higher vulnerability of this subgroup of people.

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

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

Unfortunately, there is very little high-quality evidence to guide ARV prescriptions for the elderly HIV population, particularly those with MM, because these patients are generally excluded from clinical trials.

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

People exposed to HIV for more than 10 years had a higher probability for NRTI-sparing regimens. In this subgroup, the duration of HIV exposure may be a proxy for comorbidities, but these individuals are more likely to have an issue related to NRTI resistance, mainly generated in the pre and early HAART era.
Age was the only identified independent risk factor for boosted-free regimen. Clinicians may in fact be worried of the pharmacy-dynamic behavior of drugs in ageing metabolism.

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

ARV tailoring may also consider PP interventions. Although ‘de-prescribing’ is relatively new to HIV medicine, the use of tools such as the Beers criteria, IPET(Improving Prescribing in the Elderly Tool) and STOPP-START
Criteria to tailor therapy and reduce harmful PP are well-established in gerontology practice, and should be extended to the HIV field. Italian data on dual therapies based on boosted PI are available in some clinical settings and these strategies are used in 6.7-12.8% of patients.

Conclusions

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

Funding

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Conflict of Interest

SN received travel grants and speaker’s honoraria from Gilead, Viiv, Janssen-Cilag and MSD. AC received grants, travel grants and speaker’s honoraria from Abbvie, BMS,
Gilead, Viiv, Janssen-Cilag and MSD. EF received travel grants or speakers honoraria from BMS, Gilead, Janssen-Cilag, MSD, Viiv Healthcare and consultancy fees from Gilead, Janssen-Cilag, Viiv Healthcare and BMS. GDS received travel grants from Abbvie, BMS, Gilead, Viiv, Janssen-Cilag and MSD. AMC received grants and speaker’s honoraria from Abbvie, BMS, Gilead, Viiv, Janssen-Cilag and MSD. BMC received grants and speaker’s honoraria from Abbvie, BMS, Gilead, Viiv, Janssen-Cilag and MSD. GG received travel grants and speaker’s honoraria from Abbvie, BMS, Gilead, Viiv, Janssen-Cilag and MSD. AZ, LM, SP and EG reported no potential conflict of interest.

Transparency declaration.

This work has been possible thanks to an unconditional grant by ViiV Healthcare within the Ageing & Frailty Working Group.

Acknowledgements

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=1222)</th>
<th>LDR (n=390, 31.91%)</th>
<th>MDR (n=832, 68.09%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F)</td>
<td>205 (16.3%)</td>
<td>59 (15.13%)</td>
<td>138 (16.59%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70 (68-74)</td>
<td>71.28 (4.22)</td>
<td>71.12 (4.01)</td>
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<tr>
<td>HBV co-infection</td>
<td>103 (9.83%)</td>
<td>33 (10.58%)</td>
<td>68 (9.58%)</td>
<td>0.7</td>
</tr>
<tr>
<td>HCV co-infection</td>
<td>141 (12.57%)</td>
<td>45 (13.35%)</td>
<td>91 (11.99%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Age at HIV diagnosis (years)</td>
<td>54.03 (8.83)</td>
<td>52.7 (9.02)</td>
<td>54.51 (8.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HIV duration (years)</td>
<td>17.17 (7.65)</td>
<td>18.55 (7.83)</td>
<td>16.62 (7.45)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>263 (21.23%)</td>
<td>71 (18.39%)</td>
<td>182 (22.11%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>10-20 years</td>
<td>561 (45.28%)</td>
<td>154 (39.9%)</td>
<td>247 (30.01%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;20 years</td>
<td>CD4 Nadir</td>
<td>Current CD4</td>
<td>CD4 / CD8</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-------------</td>
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<tr>
<td></td>
<td>415 (33.49%)</td>
<td>197.5 (84-310)</td>
<td>644.58 (289.04)</td>
<td>0.97 (1.45)</td>
</tr>
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<td></td>
<td>161 (41.71%)</td>
<td>214 (101-308.5)</td>
<td>655.59 (290.82)</td>
<td>1.09 (2.46)</td>
</tr>
<tr>
<td></td>
<td>247 (30.01%)</td>
<td>190 (78-307)</td>
<td>638.06 (287.59)</td>
<td>0.92 (0.55)</td>
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<td>190 (78-307)</td>
<td>0.79</td>
<td>0.12</td>
<td>0.45</td>
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</table>
Figure 1: ARV prescription strategies.
Figure 2: ARV prescription strategies according to: panel (a) duration of HIV infection (categorized in three intervals: < 10, 10 - 20 and > 20 years); panel (b) association between MM and PP.
Figure 3: Top 10 prescribed ARV in MDR and LDR

(a) MONO DUAL - ARV Combination

(b) TRIPLE MEGA - ARV Combination

# ARV Combination 68 on 384 patients

# ARV Combination 113 on 839 patients

(c) MONO DUAL - ARV Classes

(d) TRIPLE MEGA - ARV Classes

# ARV Classes 17 on 384 patients

# ARV Classes 34 on 839 patients
Figure 4: Multivariate logistic regression for the use of non-conventional ARV strategies: (panel a) mono and dual combination of therapy; (panel b) NRTI-sparing therapy; (panel c) TDF-sparing regimen; (panel d) boosted-free therapy.