Frailty and age are independently associated with patterns of HIV antiretroviral use in a clinical setting

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Potential conflicts of interest

- Research funding: Janssen, Gilead, MSD, BMS

- Consultancies: Gilead, MSD, ViiV

- Lectures: Bristol-Myers Squibb, Gilead, Janssen, MSD, ViiV

- Advisory boards: Gilead, MSD

- Travel: BMS, Gilead, MSD, ViiV
Background

Guidelines recommend antiretroviral (ARV) regimens according to viral rebound, immune depletion, or clinical sequelae.

Among HIV-positive persons with undetectable viral load and satisfactory immune status, clinicians might make prescribing decisions based on other factors, including clinical assessment regarding overall health (i.e. frailty), age, or gender.

Frailty is emerging as an important clinical condition in HIV patients on effective HAART.
What do the HIV guidelines recommend for FEMALE patients?

**DHHS:** The indications for initiation of antiretroviral therapy (ART) and the goals of treatment are the same for HIV-infected women as for other HIV-infected adults and adolescents (AI). Specific concern are related to EFV use and the risk of drug-drug interaction with oral contraceptives.

**EACS:** EFV: not recommended to be initiated in pregnant women or women with no reliable and consistent contraception; NVP: Use with extreme caution in women with CD4 counts > 250 cells/μL.

**BHIVA:** We recommend therapy-naïve HIV-positive women who are not pregnant start ART according to the same indicators as in men.

**IAS-USA:** Patients at elevated risk for fracture (e.g., postmenopausal women, known osteoporosis, or chronic hepatitis C virus [HCV] infection), avoiding tenofovir, especially in combination with a boosted PI, may be prudent.

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What do the HIV guidelines recommend for OLDER patients?

**DHHS:** >50 years:
Start ART regardless of CD4 because of increased risk of non-AIDS related complications and reduced immunological response
Bone, kidney, metabolic, CV, and liver health of older HIV-infected adults should be monitored closely

**EACS:** CVD risk assessment (Framingham score) should be performed in all men >40 and women >50 years
Bone disease assessment with FRAX in patients >40 years

**BHIVA:** Consideration should be given to starting at higher CD4 cell counts (i.e. ≥350 cells/mm³) in older persons

**IAS-USA:** Start ART if >60 years regardless of CD4 cell count

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What do the HIV guidelines recommend for FRAIL patients?


CV: cardiovascular; FRAX: WHO Fracture Risk Assessment Tool
Management of “special populations” with HIV

### Disease-Specific Considerations and Evidence Ratings for Use of Specific Antiretroviral Agents in HIV Patients With Selected Comorbidities

<table>
<thead>
<tr>
<th>Disease</th>
<th>Disease-Specific Considerations</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal insufficiency</td>
<td>Consider <strong>avoiding tenofovir</strong> because it may be associated with progression of chronic kidney disease</td>
<td>BIII&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Osteoporosis, fragility fractures</td>
<td>Consider <strong>avoiding tenofovir</strong> because it may be associated with greater decrease in bone mineral density</td>
<td>BIII&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Consider <strong>avoiding abacavir</strong>, ritonavir-boosted lopinavir, or ritonavir-boosted fosamprenavir</td>
<td>BIII&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Depression, sleep disturbance</td>
<td>Consider <strong>discontinuation of efavirenz</strong> if sleep disturbance or depression persist while receiving this agent</td>
<td>AIII&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>End-stage liver disease</td>
<td><strong>Avoid nevirapine</strong>; and <strong>use protease inhibitors with caution</strong></td>
<td>CIII&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Use <strong>ritonavir-boosted protease inhibitors and efavirenz-based regimens with caution</strong> due to development or worsening of hyperlipidemia</td>
<td>AIII&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>HIV-hepatitis B virus coinfection</td>
<td>Nucleoside component of initial therapy <strong>should include tenofovir and either emtricitabine or lamivudine</strong> in HIV-HBV coinfection infection</td>
<td>AI-BI&lt;sup&gt;b,c,d&lt;/sup&gt;</td>
</tr>
<tr>
<td>HIV-tuberculosis coinfection</td>
<td><strong>Efavirenz is the preferred NNRTI</strong> component of an antiretroviral regimen in patients receiving concurrent rifampin-based tuberculosis therapy</td>
<td>AI&lt;sup&gt;b,c,d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td><strong>Early initiation of antiretroviral therapy</strong> may delay or treat HIV-associated neurocognitive disorder</td>
<td>BII&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Objective

➢ To describe patterns of ARV use both in terms of drugs class and regimen, in relation to frailty, age or gender in a clinical setting in patients with well controlled HIV infection.

➢ To describe the impact of frailty, age or gender as determinants of ARV drugs class switching in patients with well controlled HIV infection.
Methods

➢ Retrospective observational study

➢ Participants:
  • Community-dwelling people living with HIV
  • Recruited from the Modena HIV Metabolic Clinic from 2005 to 2014
  • HAART (>1 year)
  • Suppressed HIV-RNA viral load
  • Baseline CD4>500/μL

➢ Measures (at most recent visit):
  ARV drug class exposure:
  • NNRTI current exposure
  • PI current exposure
  • INSTI current exposure

ARV regimen exposure:
  • Mega-Tx
  • Triple-Tx
  • Dual-Tx
  • Mono-Tx
  • NRTI sparing-Tx

➢ Covariates
  • Gender
  • Age
  • Frailty (45-variables frailty index)
FRAILTY RECOGNITION IN CLINICAL PRACTICE from conceptualization to measurement

Frailty as a deficit accumulation

- Frailty can be operationalized as deficit accumulation and can be expressed in a frailty index
- A frailty index derived from routinely collected clinical data can offer insights into the biology of aging using mathematics of complex systems
- Can be summarized as a scale from robust to terminally ill

Rockwood et al. Lancet 1999;353:205-6

Risk prediction

Trajectories of changes in the health status (Health transitions)
**Health variables included in the frailty indices**

**Frailty index deficits**

<table>
<thead>
<tr>
<th>No.</th>
<th>Variable</th>
<th>Frailty index deficits</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lipatrophy</td>
<td>Abnormal parathyroid hormone</td>
</tr>
<tr>
<td>2</td>
<td>Lipohypertrophy</td>
<td>Elevated D-dimer</td>
</tr>
<tr>
<td>3</td>
<td>Non-alcoholic fatty liver disease</td>
<td>Elevated C-reactive protein</td>
</tr>
<tr>
<td>4</td>
<td>Menopause or male hypogonadism</td>
<td>Sedentary lifestyle</td>
</tr>
<tr>
<td>5</td>
<td>High or low body mass index</td>
<td>Atherosclerosis</td>
</tr>
<tr>
<td>6</td>
<td>High waist circumference</td>
<td>Hyponatremia</td>
</tr>
<tr>
<td>7</td>
<td>High VLDL</td>
<td>Proteinuria or albuminuria</td>
</tr>
<tr>
<td>8</td>
<td>Sarcopenia</td>
<td>Elevated aspartate transaminase</td>
</tr>
<tr>
<td>9</td>
<td>Insulin</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>High blood glucose</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>High triglycerides</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Low high density lipoprotein</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Abnormal creatinine</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Abnormal sodium</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Abnormal potassium</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Abnormal phosphorus</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Abnormal thyroid stimulating hormone</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Anemia</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Hepatitis C co-infection</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Hepatitis B co-infection</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Vitamin D insufficiency</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Polypharmacy</td>
<td></td>
</tr>
</tbody>
</table>

Each variable included in the FI was recoded with values of 1 when a deficit was present and 0 when absent. If a variable had a missing value, it was removed from both the numerator and denominator of the FI. Observations were included if they had at least 80% of available health variables at that visit.

**Comorbidities**

- Cardiovascular disease
- Pulmonary disease
- Osteoporosis
- Cancer
- Pre-HAART start
- History of AIDS
- ART failure

**HIV covariates**

<table>
<thead>
<tr>
<th>No.</th>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Current CD4 cell count</td>
</tr>
</tbody>
</table>

**Frailty indexes:**

1. MMF Index (no comorbidities) - 37 variables
2. HIV MMFI Index (no comorbidities + HIV) - 45 variables
3. NICM FI Index (comorbidities) - 45 variables
4. HIV NICM FI Index (comorbidities + HIV) - 53 variables

The frailty index translates the “analog” conceptualization of “global clinical evaluation” into a “digital signal” (D. Kotler).
### Results

#### Demographic and HIV characteristics

<table>
<thead>
<tr>
<th>Patients</th>
<th>1202</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean±SD)</td>
<td>50 ±7</td>
</tr>
<tr>
<td>Women (n [%])</td>
<td>383 (32)</td>
</tr>
<tr>
<td>Duration HIV months (Median IQR)</td>
<td>153 (100 – 196)</td>
</tr>
<tr>
<td>Nadir CD4 (Median IQR)</td>
<td>209 (101 – 300)</td>
</tr>
<tr>
<td>Current CD4 (Median IQR)</td>
<td>721 (610 – 893)</td>
</tr>
<tr>
<td>Frailty index (Mean±SD)</td>
<td>0.30 ±0.09</td>
</tr>
<tr>
<td>Multi-morbidity (n [%])</td>
<td>357 (30)</td>
</tr>
</tbody>
</table>

#### Prevalence of HANA conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>n [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease (n [%])</td>
<td>73 (6)</td>
</tr>
<tr>
<td>Hypertension (n [%])</td>
<td>504 (42)</td>
</tr>
<tr>
<td>Diabetes (Type II) (n [%])</td>
<td>155 (13)</td>
</tr>
<tr>
<td>Chronic Kidney disease (n [%])</td>
<td>123 (10)</td>
</tr>
<tr>
<td>COPD (n [%])</td>
<td>46 (4)</td>
</tr>
<tr>
<td>Osteoporosis (n [%])</td>
<td>285 (24)</td>
</tr>
<tr>
<td>Cancer (n [%])</td>
<td>50 (4)</td>
</tr>
</tbody>
</table>

#### ARV drug class exposure (most recent visit)

- **NNRTI; 409; 37%**
- **PI; 455; 41%**
- **INSTI; 241; 22%**

#### ARV regimen current exposure (most recent visit)

- **Mega-Tx; 161; 14%**
- **Triple-Tx; 897; 75%**
- **Dual-Tx; 88; 7%**
- **Mono-Tx; 44; 4%**

#### NRTI-sparing

- **NRTI-backbone; 1190; 89%**
- **NRTI-sparing; 147; 11%**
Age and frailty spectrum in different ARV drug classes current exposure

- **NNRTI-based regimen**: 409 pts
- **PI-based regimen**: 455 pts
- **INSTI-based regimen**: 241 pts
## Age and frailty spectrum in different ARV regimen current exposure

<table>
<thead>
<tr>
<th>ARV Regimen</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple-Tp</td>
<td>897 pts</td>
</tr>
<tr>
<td>Mega-Tp</td>
<td>161 pts</td>
</tr>
<tr>
<td>Dual-Tp</td>
<td>88 pts</td>
</tr>
<tr>
<td>NRTI-Spearing-Tp</td>
<td>147 pts</td>
</tr>
<tr>
<td>Mono-tp</td>
<td>44 pts</td>
</tr>
</tbody>
</table>

### Breakdown by Age and Frailty Spectrum

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Frailty Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;46</td>
<td></td>
</tr>
<tr>
<td>47-50</td>
<td></td>
</tr>
<tr>
<td>51-54</td>
<td></td>
</tr>
<tr>
<td>&gt;55</td>
<td></td>
</tr>
</tbody>
</table>

- **<0.23**
- **0.24-0.29**
- **0.30-0.36**
- **0.37**

### Frailty Spectrum

- **0**
- **2**
- **4**
- **6**
- **8**
- **10**
- **12**

- **15**
- **20**

### Age Breakdown

- **<46**
- **47-50**
- **51-54**
- **>55**
Multinomial logistic regression to identify predictors of ARV drug class current exposure

- Age, per 10 yrs
- Men vs. Women
- Frailty Index, per 0.1
- CD4 nadir <200 cell/μL
- Multimorbidity

RRR: 1.4, 95% CI 1.14–1.71
RRR: 1.46, 95% CI 1.23–1.73
Multinomial logistic regression to identify predictors of ARV regimen current exposure

RRR: 1.58, 95% CI 1.13–2.21
Logistic regression to identify predictors of NRTI-spearing regimen current exposure

- Age, per 10 yrs: OR=1.41, 95% CI 1.08–1.83
- Men vs. Women
- Frailty Index, per 0.1
- CD4 nadir <200 cell/μL
- Multimorbidity

OR (95% CI)
Cox regression analysis for factors associated with ARV class switch

Predictors of ARV drugs switching to PI

- Age, per 10 yrs
- Men vs. Women
- Frailty Index, per 0.1
- CD4 nadir <200 cell/µL
- Multimorbidity

Predictors of ARV drugs switching to INSTI

- Age, per 10 yrs
- Men vs. Women
- Frailty Index, per 0.1
- CD4 nadir <200 cell/µL
- Multimorbidity

- 45 cases who switched to PI
- 402 controls non on PI who did not switch
- 117 cases who switched to INSTI
- 689 controls non on INSTI who did not switch

No difference were present in demographic and HIV variables between cases and controls.
Limitations

• The retrospective nature of the study limits the possibility to explore a causal relationship between gender, age, and frailty and pattern of ARVs use.
• INSTI class is limited to raltegravir, this drug was introduced in the Italian market in 2011.
• In Italy ARV are distributed free of charge, the different prices of ARV drugs play a role in prescription attitudes of clinicians. The impact of drug costs was not included in this analysis.
• ARV pill burden was not included as a confounder.
• Lack of external validation of Frailty Index in an independent HIV cohort.
Discussion

• Differences in patterns of ARV use were observed in relation to gender, age and frailty.
  – Women are more likely to switch to INSTI based regimens.
  – Older age is associated with “unconventional” ARV regimen (Dual-Tx, NRTI-sparing regimen) and less likely associated with PI switch.
  – Frailty discriminates PI and INSTI exposure from NRTI

• This study shows a clinical attitude towards ARV selection that may incorporates global judgment about overall health status and vulnerability beyond traditional virological and immunological markers of HIV disease
RCTs and FI
future directions

Future ARV randomized clinical trials may consider frailty index as an inclusion criteria for the selection of a vulnerable population to address specific ARV regimens/strategies.

Future ARV randomized clinical trials may include frailty index as a clinical endpoint to prove the value of specific ARV regimens/strategies.
Acknowledgment

Zona S, Stentarelli C., Carli F., Malagoli A., Mussini C.

Falutz J

Brothers TD, Theou O., Kirkland S, Rockwood K