A Bidirectional Multi-State Model for Panel Data on Bone Mineral Density among HIV-Infected Patients

Klaus Langohr\textsuperscript{1}  Guadalupe Gómez\textsuperscript{1}  Nuria Pérez\textsuperscript{1, 2}  Eugenia Negredo \textsuperscript{2}  Anna Bonjoch \textsuperscript{2}

\textsuperscript{1}Universitat Politècnica de Catalunya, Barcelona, Spain

\textsuperscript{2}Fundació Lluita contra la SIDA, Badalona, Spain

6\textsuperscript{th} March, 2018
Outline

1 Bone Mineral Density

2 Goals of the Present Study

3 Data Set on Bone Mineral Density

4 A Multi-State Model With Panel Data

5 Conclusions and Final Remarks
Bone Mineral Density (BMD)

BMD Test:
- Dual-energy x-ray absorptiometry (DXA) test measures BMD at hip and spine and compares it to established norms.

T-score:
- Comparison to 30-years-old healthy person (same gender).

Classification:
- T-score Diagnosis
  - $T \geq -1$: Normal
  - $-1 > T \geq -2.5$: Osteopenia
  - $T < -2.5$: Osteoporosis

Source:
NIH Osteoporosis and Related Bone Diseases National Resource Center.

Langohr et al. (UPC & FLS)
Reunió GRBIO
6th March, 2018
Bone Mineral Density (BMD)

BMD Test:
Dual-energy x-ray absorptiometry (DXA) test measures BMD at hip and spine and compares it to established norms.

\[ \text{T-score: Comparison to 30-years-old healthy person (same gender).} \]
Bone Mineral Density (BMD)

BMD Test:
Dual-energy x-ray absorptiometry (DXA) test measures BMD at hip and spine and compares it to established norms.

$\Rightarrow$ **T-score**: Comparison to 30-years-old healthy person (same gender).

Classification:

<table>
<thead>
<tr>
<th>T-score</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T \geq -1$</td>
<td>Normal</td>
</tr>
<tr>
<td>$-1 &gt; T \geq -2.5$</td>
<td>Osteopenia</td>
</tr>
<tr>
<td>$-2.5 &gt; T$</td>
<td>Osteoporosis</td>
</tr>
</tbody>
</table>

Source:
NIH Osteoporosis and Related Bone Diseases National Resource Center.

Langohr et al. (UPC & FLS)

Reunió GRBIO

6th March, 2018

2 / 29
Bone Mineral Density (BMD)

BMD Test:
Dual-energy x-ray absorptiometry (DXA) test measures BMD at hip and spine and compares it to established norms.

$\sim$ T-score: Comparison to 30-years-old healthy person (same gender).

Classification:

<table>
<thead>
<tr>
<th>T-score</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T \geq -1$</td>
<td>Normal</td>
</tr>
<tr>
<td>$-1 &gt; T \geq -2.5$</td>
<td>Osteopenia</td>
</tr>
<tr>
<td>$-2.5 &gt; T$</td>
<td>Osteoporosis</td>
</tr>
</tbody>
</table>

Source: NIH Osteoporosis and Related Bone Diseases National Resource Center.
Study Goals

Main objective:
Assess the evolution of BMD as a function of age in a cohort of HIV-infected patients.

In particular:
Determine risk factors for progression of bone loss to osteopenia and osteoporosis.

Study the impact of antiretrovirals on BMD.

Available Information:
T-scores from femur (neck, trochanter, total) and lumbar region (L1-L4).

Focus:
Evolution of minimum T-score (MTS) among femur and lumbar region.
**Study Goals**

**Main objective:**
Assess the evolution of BMD as a function of age in a cohort of HIV-infected patients.
**Study Goals**

**Main objective:**
Assess the evolution of BMD as a function of age in a cohort of HIV-infected patients.

**In particular:**
- Determine risk factors for progression of bone loss to osteopenia and osteoporosis.
- Study the impact of antiretrovirals on BMD.
**Study Goals**

**Main objective:**
Assess the evolution of BMD as a function of age in a cohort of HIV-infected patients.

**In particular:**
- Determine risk factors for progression of bone loss to osteopenia and osteoporosis.
- Study the impact of antiretrovirals on BMD.

**Available Information:**
T-scores from femur (neck, trochanter, total) and lumbar region (L1-L4).

**Focus:**
Evolution of minimum T-score (MTS) among femur and lumbar region.
Data Set of the Fundació Lluita contra la SIDA

Complete data set:

- 4335 DXA scans of 1484 patients from 1999 to 2016.
- Males: 75.4%.
- Age at 1st DXA scan:
  - Mean: 42.8
  - Median: 42.4
  - Range: 17–78
- DXA scans per person:
  - Mean: 2.9
  - Median: 2
  - Range: 1–18
- BMD at 1st DXA scan:
  - Normal BMD: 34.2%
  - Osteopenia: 52.0%
  - Osteoporosis: 13.8%
Data Set of the Fundació Lluita contra la SIDA

Complete data set:
- 4335 DXA scans of 1484 patients from 1999 to 2016.
- Males: 75.4%.
- Age at 1st DXA scan:
  - Mean: 42.8
  - Median: 42.4
  - Range: 17.4 – 78.3

Langohr et al. (UPC & FLS)  
Reunió GRBIO  
6th March, 2018
Data Set of the Fundació Lluita contra la SIDA

Complete data set:

- 4335 DXA scans of 1484 patients from 1999 to 2016.
- Males: 75.4%.
- Age at 1st DXA scan:
  - Mean: 42.8
  - Median: 42.4
  - Range: 17.4 – 78.3
- DXA scans per person:
  - Mean: 2.9
  - Median: 2
  - Range: 1 – 18
Data Set of the Fundació Lluita contra la SIDA

Complete data set:

- 4335 DXA scans of 1484 patients from 1999 to 2016.
- Males: 75.4%.
- Age at 1st DXA scan:
  - Mean: 42.8
  - Median: 42.4
  - Range: 17.4 – 78.3
- DXA scans per person:
  - Mean: 2.9
  - Median: 2
  - Range: 1 – 18
- BMD at 1st DXA scan:
  - Normal BMD: 34.2%
  - Osteopenia: 52.0%
  - Osteoporosis: 13.8%
**Data Set of the Fundació Lluita contra la SIDA**

**Follow-up data set:**

- 3726 DXA scans of 875 patients (59%) with 2 or more DXA scans.
- Males: 75.3%.
- Age at 1st DXA scan:
  - Mean: 42.4
  - Median: 41.7
  - Range: 20.5 – 77.6
- DXA scans per person:
  - Mean: 4.3
  - Median: 3
  - Range: 2 – 18
- BMD at 1st DXA scan:
  - Normal BMD: 31.1%
  - Osteopenia: 52.2%
  - Osteoporosis: 16.7%
Follow-up Times

**Figure:** Follow-up times of 875 patients with more than 1 DXA scan.
**Follow-up Times**

**Figure:** Follow-up times of 875 patients with more than 1 DXA scan.
Multi-State Model Approach (I)
Multi-State Model Approach (I)

Multi-state process \( \{X(a), a \in A\} \) with state space

\[
S = \{0, 1, 2\} = \{\text{Normal, Osteopenia, Osteoporosis}\},
\]

where

- \( a \): patient’s age at each DXA scan,
- \( X(a) = s \in S \): patient’s state at \( a \).
Multi-State Model Approach (I)

Multi-state process \( \{X(a), a \in A\} \) with state space

\[ S = \{0, 1, 2\} = \{\text{Normal, Osteopenia, Osteoporosis}\}, \]

where

- \( a \): patient’s age at each DXA scan,
- \( X(a) = s \in S \): patient’s state at \( a \).

**Figure:** Disease progression model for bone mineral density.
Figure: Minimum T-score (MTS) over time among 24 patients.
Bone mineral density: BMD diagnostics

Diagnosis based on MTS over time
Years of follow-up
Diagnosis
Osteoporosis
Osteopenia
Normal

Figure: BMD classification over time among 24 patients.
**Multi-State Model Approach (II)**

Multi-state process \( \{X(a), a \in A\} \) with state space

\[
S = \{0, 1, 2\} = \{\text{Normal, Osteopenia, Osteoporosis}\},
\]

where

- \( a \): patient’s age at each DXA scan,
- \( X(a) = s \in S \): patient’s state at \( a \).

**Figure:** Bidirectional multi-state model for bone mineral density.
For $a, b \in A$, $a < b$, and $h, j \in S = \{0, 1, 2\}$:

- **Transition probabilities:**

  \[ P_{hj}(a, b; \mathcal{H}_{a-}) = P(X(b) = j|X(a) = h; \mathcal{H}_{a-}), \]

  where $\mathcal{H}_{a-}$ is the process history over $[0, a)$.

- **Transition intensities:**

  \[ q_{hj}(a; \mathcal{H}_{a-}) = \lim_{\Delta a \to 0} \frac{P_{hj}(a, a + \Delta a; \mathcal{H}_{a-})}{\Delta a}, \]
Model Assumption 1: Markov Model

For $a, b \in A$, $a < b$, and $h, j \in S = \{0, 1, 2\}$:

- **Transition probabilities:**

  \[ P_{hj}(a, b; \mathcal{H}_{a^-}) = P_{hj}(a, b) = P(X(b) = j | X(a) = h). \]

- **Transition intensities:**

  \[ q_{hj}(a; \mathcal{H}_{a^-}) = q_{hj}(a) = \lim_{\Delta a \to 0} \frac{P_{hj}(a, a + \Delta a)}{\Delta a}. \]
Assumption 2: Time-inhomogeneous model

For $a \in A$ and $h, j \in S = \{0, 1, 2\}$

- **Piecewise-constant transition intensities:**

$$q_{hj}(a) = \begin{cases} 
q_{hj}^0, & \text{if } a \leq 45, \\
q_{hj}^1, & \text{if } a > 45.
\end{cases}$$

- **Transition intensity matrices:**

$$Q^m = \begin{pmatrix}
-q_{01}^m & q_{01}^m & 0 \\
q_{10}^m & -q_{10}^m - q_{12}^m & q_{12}^m \\
0 & q_{21}^m & -q_{21}^m
\end{pmatrix}, \quad m \in \{0, 1\}.$$
Assumption 2: Time-inhomogeneous Model

Transition probability matrices (Kalbfleisch and Lawless, 1985):

For $a, b \in A$, $a < b \leq 45$ and $t = b - a$:

$$P(a, b) = P^1(0, t) = P^1(t) = \exp(Q^1 t) = \sum_{r=0}^{\infty} Q^1_r t^r / r!$$
Assumption 2: Time-inhomogeneous Model

Transition probability matrices (Kalbfleisch and Lawless, 1985):

- For $a, b \in A$, $a < b \leq 45$ and $t = b - a$:

  $$ P(a, b) = P^1(0, t) = P^1(t) = \exp (Q^1 t) = \sum_{r=0}^{\infty} \frac{Q^1 r t^r}{r!} $$

- For $a, b \in A$, $45 < a < b$ and $t = b - a$:

  $$ P(a, b) = P^2(0, t) = P^2(t) = \exp (Q^2 t) = \sum_{r=0}^{\infty} \frac{Q^2 r t^r}{r!} $$
Assumption 2: Time-inhomogeneous Model

Transition probability matrices (Kalbfleisch and Lawless, 1985):

- For \( a, b \in A, \ a < b \leq 45 \) and \( t = b - a \):

\[
P(a, b) = P^1(0, t) = P^1(t) = \exp (Q^1 t) = \sum_{r=0}^{\infty} Q_1^r t^r / r!
\]

- For \( a, b \in A, \ 45 < a < b \) and \( t = b - a \):

\[
P(a, b) = P^2(0, t) = P^2(t) = \exp (Q^2 t) = \sum_{r=0}^{\infty} Q_2^r t^r / r!
\]

- For \( a, b \in A, \ a \leq 45 < b \):

\[
P(a, b) = P^1(45 - a)P^2(b - 45)
\]
Panel data

(Jackson, 2011):
(. . . ) observations of a continuous-time process at arbitrary times, (. . . ).

All transition times are interval-censored.
Panel data (Jackson, 2011):

(…) observations of a continuous-time process at arbitrary times, (…).
Panel data (Jackson, 2011):

\(\ldots\) observations of a continuous-time process at arbitrary times, \(\ldots\).

All transition times are \textbf{interval-censored}:

![Graph showing the minimum T-score over time with years of follow-up and various IDs]
Likelihood function for panel data

- **Likelihood function:**
  Given \( X_i = \left( X_i(a_{i,1}), \ldots, X_i(a_{i,n_i}) \right)' \), \( i = 1, \ldots, n \):

\[
L(q) = \prod_{i=1}^{n} L_i(q) = \prod_{i=1}^{n} \prod_{j=1}^{n_i-1} P(X(a_{i,j+1}|X(a_{i,j}))
\]

where \( q = (q_{01}^0, q_{10}^0, q_{12}^0, q_{21}^0, q_{01}^1, q_{10}^1, q_{12}^1, q_{21}^1)' \).
**Likelihood function for panel data**

- **Likelihood function:**
  Given $X_i = (X_i(a_{i,1}), \ldots, X_i(a_{i,n_i}))'$, $i = 1, \ldots, n$:

  $$L(q) = \prod_{i=1}^{n} L_i(q) = \prod_{i=1}^{n} \prod_{j=1}^{n_i-1} P(X(a_{i,j+1})|X(a_{i,j})),$$

  where $q = (q_{01}^0, q_{10}^0, q_{12}^0, q_{21}^0, q_{01}^1, q_{10}^1, q_{12}^1, q_{21}^1)'$.

- **Software:** The msm Package for R (Christopher H. Jackson, 2011).
**Likelihood function for panel data**

- **Likelihood function:**
  Given $X_i = (X_i(a_{i,1}), \ldots, X_i(a_{i,n_i}))'$, $i = 1, \ldots, n$:

  $$L(q) = \prod_{i=1}^{n} L_i(q) = \prod_{i=1}^{n} \prod_{j=1}^{n_i-1} P(X(a_{i,j+1} | X(a_{i,j})),$$

  where $q = (q_{01}, q_{10}, q_{12}, q_{21}, q_{01}, q_{10}, q_{12}, q_{21})'$.

- **Software:** The msm Package for R (Christopher H. Jackson, 2011).

- **Available data:**
  
<table>
<thead>
<tr>
<th></th>
<th>$n$</th>
<th>DXA scans</th>
<th>Transitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>216</td>
<td>898</td>
<td>682</td>
</tr>
<tr>
<td>Men</td>
<td>659</td>
<td>2828</td>
<td>2169</td>
</tr>
</tbody>
</table>
Transitions Between States: Women

Figure: All transitions among female HIV-infected patients.
Transitions Between States: Men

From

Normal

Osteopenia

Osteoporosis

To

Normal

Osteopenia

Osteoporosis

Figure: All transitions among male HIV-infected patients.
**MSM (Women): Transition Intensities**

**Figure:** MSM for female HIV-infected patients: Estimated transition intensities.
Figure: Normal BMD to osteopenia and osteoporosis (Left panel: Women).
**Figure**: Osteopenia to osteoporosis (Left panel: Women).
Data on Antiretroviral (AR) Treatments

- Generally, several AR drugs per patient.
- Variable of interest: Drug intake 1 year before DXA scan.
- Protease inhibitors (PIs) are potential risk factors for bone loss.
Data on Antiretroviral (AR) Treatments

- Generally, several AR drugs per patient.
- Variable of interest: Drug intake 1 year before DXA scan.
- Protease inhibitors (PIs) are potential risk factors for bone loss.

AR intake 1 year before DXA:

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>253</td>
<td>7.2</td>
</tr>
<tr>
<td>Darunavir</td>
<td>519</td>
<td>14.8</td>
</tr>
<tr>
<td>Kaletra</td>
<td>616</td>
<td>17.5</td>
</tr>
<tr>
<td>Other PI</td>
<td>469</td>
<td>13.3</td>
</tr>
<tr>
<td>No PI</td>
<td>1659</td>
<td>47.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>3516</td>
<td>100.0</td>
</tr>
</tbody>
</table>
MSMs: Hazard Regression Models

- **Transition-specific hazard regression models:**

\[
q^m_{hj}(t; Z(t)) = q^m_{hj} \exp(\beta_{hj} Z(t)), \quad m \in \{0, 1\},
\]

where \( Z \): AR intake 1 year before DXA.
**MSMs: Hazard Regression Models**

- Transition-specific hazard regression models:

\[ q_{hj}^m(t; Z(t)) = q_{hj}^m \exp(\beta_{hj} Z(t)), \quad m \in \{0, 1\}, \]

where \( Z \): AR intake 1 year before DXA.

- Models assume \textit{exponentially} distributed sojourn times.
**MSMs: Hazard Regression Models**

- **Transition-specific hazard regression models:**

  \[ q_{hj}^m(t; Z(t)) = q_{hj}^m \exp(\beta_{hj}Z(t)), \quad m \in \{0, 1\}, \]

  where \( Z \): AR intake 1 year before DXA.

- Models assume **exponentially** distributed sojourn times.

- Fit of the model assume \( Z(t) \) is constant between observation times.
Transition-specific hazard regression models:

\[ q_{hj}^m(t; Z(t)) = q_{hj}^m \exp(\beta_{hj} Z(t)), \quad m \in \{0, 1\}, \]

where \( Z \): AR intake 1 year before DXA.

Models assume \textbf{exponentially} distributed sojourn times.

Fit of the model assume \( Z(t) \) is constant between observation times.

Effect size measure:

\[ HR = \frac{q_{hj}^m(Z(t) = z_2)}{q_{hj}^m(Z(t) = z_1)} = \exp(\beta_{hj}(z_2 - z_1)), \quad m \in \{0, 1\}. \]
**HRs associated to different PIs (Women)**

**Figure:** Estimated hazard ratios associated to PIs.
**HRs associated to different PIs (Men)**

**Figure:** Estimated hazard ratios associated to PIs.
Diagnostic Plots for Model Assessment

Figure: MSM including AR intake: Female HIV-infected patients.

Comments:
- Age periods considered: < 45, >= 45
- Midpoint imputation for transition times
**Diagnostic Plots for Model Assessment**

**Figure:** MSM including PI intake: Male HIV-infected patients.
Summary:

- Bidirectional MSM with panel data was fitted.
- PIs, especially Darunavir, seem to be a risk factor for bone loss.
- PIs seem to have slightly different effect in men than in women.
**Final Comments and Future Research**

**Summary:**
- Bidirectional MSM with panel data was fitted.
- PIs, especially Darunavir, seems to be a risk factor for bone loss.
- PIs seem to have slightly different effect in men than in women.

**Possible future research:**
- Treatment data could be modeled as cumulative exposure.
- Try alternatives to exponential distribution for sojourn times.
- Use of other goodness-of-fit tools.
- Test for Markov assumption with panel data.
Thank you very much!