Influence of Transmitted CD4 Decline due to ART on HIV Negative Patients

Anna Schultze 1, Carlo Torti 2, Alessandro Cozzi-Leprì 1, Anne-Mieke Vandamme 1,3, Maurizio Zazzi 2, Helen Sambatakou 14, Andrea De Luca 1, Anna Maria Geretti 1,5, Anders Sonnerborg 3 and Giuseppe Lapadula 10

1. Department of Infectious and Paediatric Health, University College London, London, UK; 2. Unit of Infectious and Tropical Diseases, Department of Medical and Surgical Sciences, University "Maglie Graniti", Catanzaro, Italy; 3. KI Course – University of Cambridge, Rega Institute for Medical Research, Leuven, Belgium; 4. Instituto de Salud Pública y Medico Tropical, Universidad Navarra de Logroño, Logroño, Spain; 5. University of Siena, Siena, Italy; 6. Hippokration General Hospital, University of Athens, Athens, Greece; 7. University Division of Infectious Diseases, Siena University Hospital, Siena, Italy; 8. University of Liverpool, Liverpool, UK; 9. Karolinska Institute, Stockholm, Sweden; 10. Dipartimento S. Gerardo, Monza, Italy

Introduction

1. Transmitted drug resistance mutations (TDRM) may lead to an altered progression of HIV disease before the start of antiretroviral therapy (ART).

2. Existing research into the effect of the effect of TDRM on the natural history of HIV has found conflicting results.

Aim:

1. To investigate the effect of TDRM on CD4 count changes before the start of ART.

Methods

Data and Study population

Data from several European HIV clinics (VN-AB, Eufasia and EuroSIDA contributing clinics; Royal Free and St Mary’s Hospital, London; University of Barà were merged. Individuals were included if they:

1. Were older than 18 years old.

2. Had at least 1 CD4 count available.

3. Had at least 1 genotypic resistance test before starting ART (first date any ART drug was initiated).

4. Had data available for the viral set point to be estimated.

FU lasted until the last CD4 measurement before ART. Baseline was defined as the date of the first available CD4 count. TDRM were identified using the WHO 2009 surveillance list. We presumed that mutations detected at any time during follow-up had been present since baseline, and for those with more than one pre-ART resistance test available resistance was considered in a cumulative manner. The set point was defined as the median of all pre-ART viral load measurements.

Statistical methods

Linear mixed models with a random intercept and slope were used to estimate the effect of TDRM on CD4 slopes. The 10 most commonly detected mutations were tested for their effect on CD4 slopes; for these comparisons we used a Bonferroni corrected p-value threshold of 0.005 to indicate statistical significance.

Sensitivity analyses:

1. The analyses were repeated stratified by subtype B and non-B.

2. The analyses were repeated using the minimum available date for each person as the baseline date, restricting the analyses to those who had this information available (N=1285).

Results

Baseline characteristics of the study population, according to TDRM

<table>
<thead>
<tr>
<th>TDRM absence</th>
<th>Any TDRM</th>
<th>Wild-type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N (%)</td>
<td>14.58 (14.2)</td>
<td>14.58 (14.8)</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>47.04 (45.3-48.6)</td>
<td>47.04 (45.3-48.6)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>51.12 (51.3)</td>
<td>51.12 (51.3)</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm³)</td>
<td>506 (494-518)</td>
<td>506 (494-518)</td>
</tr>
<tr>
<td>Plasma viral load (cpg/ml)</td>
<td>77 (76-80)</td>
<td>77 (76-80)</td>
</tr>
</tbody>
</table>

Baseline characteristics of the study population, according to TDRM

<table>
<thead>
<tr>
<th>TDRM absence</th>
<th>Any TDRM</th>
<th>Wild-type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N (%)</td>
<td>14.58 (14.2)</td>
<td>14.58 (14.8)</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>47.04 (45.3-48.6)</td>
<td>47.04 (45.3-48.6)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>51.12 (51.3)</td>
<td>51.12 (51.3)</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm³)</td>
<td>506 (494-518)</td>
<td>506 (494-518)</td>
</tr>
<tr>
<td>Plasma viral load (cpg/ml)</td>
<td>77 (76-80)</td>
<td>77 (76-80)</td>
</tr>
</tbody>
</table>

Sensitivity analyses:

The results from sensitivity analyses can be seen in Table 2. When restricting the analysis to individuals with subtype B viruses only, there was still evidence to suggest that the presence of any TDRM was associated with a decline in CD4 counts (p<0.05). Using the minimum date available as the baseline date did not change the overall conclusions.

Limitations

Date of Serosconversion: Due to data availability, we could not use the date of serosconversion as the baseline date. CD4 count trends may differ according to time since serosconversion.

Generalizability: Individuals with a resistance test before starting treatment may differ from individuals not tested. Despite the large dataset our analysis may have suffered from a lack of power.

Conclusions and Future Work

We were not able to find convincing evidence supporting the hypothesis that the rate of CD4 decline in the absence of ART is different between patients with and without TDRM.

This could reflect the fact that mutations with less impact on fitness are preferentially transmitted.

We cannot rule out the fact that TDRM may influence the rate of CD4 decline differently in different time periods since serosconversion.

Future work will focus on characterising viral load changes over time, describing associations between TDRM and viral load changes and evaluating our assumption that mutations persisted throughout FU in sensitivity analyses.

Residual prevalence

Resistance was detected in 9.7% of individuals; 6.9% had NRTI resistance, 3% NRTI resistance and 2.5% PI resistance. The 10 most commonly detected mutations and their prevalence can be seen in Figure 1.

The effect of TDRM on CD4 count changes before the start of ART

The overall estimated CD4 decline was -54 cells/mm³/year (95%CI = -56, -52). In univariable analyses, we found no evidence that CD4 decline differed according to the presence of any TDRM compared to wild-type (Table 1). There was also no evidence that CD4 count decline differed among individuals with NRTI or PI resistance as compared to those with wild-type viruses. There was some weak evidence suggesting that CD4 slopes declined more steeply among individuals with detected NNRTI resistance (difference compared to wild-type: -12 (95%CI=-25,-2) cells/mm³/year; p<0.001). These conclusions did not change upon adjustment for covariates including viral load set point (Table 2).

Associations between individual TDRM and CD4 count changes before the start of ART

The associations between individual TDRM and CD4 slopes can be seen in Table 3. There was some suggestion that CD4 slopes were less marked among individuals who had the T215Y mutation (difference compared to wild-type: +35 (95%CI=+15,+56) cells/mm³/year) but more marked among individuals who had the revertant T215D mutation (difference compared to wild-type: -39 (95%CI=-91,+5) cells/mm³/year) however, this was not the case for T215S. There was no evidence of an association between the M184V and CD4 count declines (difference compared to wild-type: +0.3 (-19,+20) cells/mm³/year).

Sensitivity analyses

The results from sensitivity analyses can be seen in Table 4. When restricting the analysis to individuals with subtype B viruses only, there was still evidence to suggest that the presence of any TDRM was associated with a decline in CD4 counts (p<0.05). Using the minimum date available as the baseline date did not change the overall conclusions.

References:


Download poster at: www.cphiv.dk