Aging and comorbidities in the Swiss HIV Cohort Study

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Kantonsspital Baselland, University of Basel, Switzerland

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Aging and comorbidities in the Swiss HIV Cohort Study

1) Introduction: The Swiss HIV Cohort Study

1) Genetic studies of metabolic/aging-related conditions

1) Obesity

1) Bone health

1) Comparison with HIV-negative population
The Swiss HIV Cohort Study (SHCS)

• Established in 1988
• Total enrollment: 18092 participants as of 9/2013

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- Established in 1988
- Total enrollment: 18092 participants as of 9/2013
- Enrolment ongoing: ≈ 500 new patients registered per year

Figure 1: Patients newly registered each year in the Swiss HIV Cohort Study (SHCS), 1984-2012
SHCS: 8’711 participants actively followed

- 75% of HIV+ patients treated with ART in Switzerland
- 29% women
- 66% caucasian
- HIV acquisition
  - 35% MSM
  - 32% hetero
  - 29% IDU


www.shcs.ch
SHCS Infrastructure / Procedures

• 2 SHCS visits / year: questionnaire + lab

• 1 stored plasma + cell sample / year → frozen aliquots

• genetic consent: 97% of participants
SHCS Budget

- current budget approx. 3.2 million $/year

- **infrastructure**: 2,600,000 $/year
- **research projects**: 600,000 $/year

- Initially funded by Swiss Federal Office of Public Health

  → since 2000 funded by Swiss National Research Foundation (SNF; "Swiss NIH")

- External funding of individual research projects (SNF, other)
SHCS Core Research Projects

- Genetics core project (2003)
- Resistance core project (2005)
- Metabolics and aging core project (2013)

Private physicians
Smaller hospitals

Data center

Clinics
Laboratories
Biobanks
The SHCS Core Project

Metabolism and Aging

• First patient enrolled: August 2013

• Inclusion: Age >45

• **Goal**: collect aging-related information in a standardized fashion
  • DXAs (n=1000)
  • Neurocognitive testing (n=1000)
  • Coronary CT angiography (CCTA) + Calcium score (n=418)
  • Genetic testing
  • Fasting urine and plasma (n=2000)

Testing battery based on START trial
... in the interest of generating data that can be internationally compared

So far, no frailty assessments and no biomarkers
Research in the SHCS (N=18’092 participants, 8’711 active)

**COURSE OF HIV DISEASE**

**OPPORTUNISTIC INFECTIONS**  
- n=12’223

**DEATHS**  
- n=4’692

**ACUTE HIV INFECTION: PATHOGENESIS & TREATMENT**  
- 936 primary HIV infections

**PRE-ART PHASE: THE NATURAL HISTORY OF HIV DISEASE**  
- 19’007 HIV Genomes and 2’500 host genomes: The Genetic Core Project

**ART PHASE: COURSE AND OUTCOMES OF TREATED HIV-INFECTION**

- **ART efficacy**: 26’973 HIV drug levels: The HIV Resistance Core Project
- **Drug toxicity**: 11’337 treatment interruptions due to side effects

- **Co-morbidities, Aging and neurocognitive disorders**:
  - 586 cardiovascular events, 2’421 cancers: The Metabolic and Aging project
  - 1’000 neurocognitive assessments planned: The NAMACO project

- **Coinfections**
  - 3’557 Hepatitis C, 7’033 Hepatitis B, 2’658 Syphilis: The co-infection project

- **Pregnancy and pediatric**: 978 deliveries, The Mother+Child HIV Cohort Study

- **Psychosocial effects and health care usage**: 8’711 active participants

Slide: Huldrych Günthard, Andri Rauch
With successful ART, HIV+ persons are aging ....

Source: SHCS 05/2013
With successful ART .... HIV+ persons are aging ... and are experiencing more co-morbidities

Hasse CID 2011
With successful ART .... HIV+ persons are aging ... and are experiencing more co-medications

against what? Hypertension, Dyslipidemia, Diabetes, Depression ....

Hasse CID 2011
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Contribution of Genetic Background, Traditional Risk Factors, and HIV-Related Factors to Coronary Artery Disease Events in HIV-Positive Persons

Genetics of Coronary Artery Disease (CAD) in the general population

Meta-analysis of 14 genome wide association studies (GWAS): 23 common SNPs associated with CAD

Schunkert Nature Genetics 2011
The MAGNIFICENT Consortium

TOTAL: 24 HIV observational studies

571 HIV+ CAD cases

1,304 HIV+ controls without CAD events, matched on gender and cohort

Rotger CID 2013
Genotyping: 
HumanCardio-Metabo BeadChip® (Illumina)

✓ a custom array of **196,725 SNPs** from gene regions associated with multiple metabolic/cardiovascular traits.

✓ designed by representatives of 7 GWAS meta-analysis consortia.

Preuss et al (CARDIoGRAM) Circulation Cardiovasc Genet 2010
Joint consideration of all factors relevant to CAD: Comparative effect sizes of traditional, HIV-related, genetic risk
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Comparative effect sizes of traditional, HIV-related, genetic risk

Rotger M, MAGNIFICENT Consortium, INSIGHT, Swiss HIV Cohort Study, CID 2013
Joint consideration of all factors relevant to CAD: Comparative effect sizes of traditional, HIV-related, genetic risk

- Genetic Score
- HIV-related factors:
  - CD4
  - HIV RNA
  - INDINAVIR ≥ 1 year of exposure
  - LOPINAVIR ≥ 1 year of exposure
  - on ART
  - ABACAVIR current exposure
- Traditional CAD risk factors:
  - LOW HDL CHOLESTEROL
  - HYPERTENSION
  - HIGH CHOLESTEROL
  - PAST SMOKING
  - DIABETES
  - FAMILY HISTORY OF CAD
  - AGE per 5 years
  - CURRENT SMOKING

Rotger M, MAGNIFICENT Consortium, INSIGHT, Swiss HIV Cohort Study, CID 2013
Diabetes risk in HIV+ according to genetic background

GWAS in general population: 22 common SNPs associated with diabetes

This study: n=94 white SHCS participants with new onset diabetes 2000-2009, n=550 SHCS controls without diabetes

≈20% of patients have unfavorable genetic background → relative risk of diabetes = 2.74

Genetic background explains far more of the diabetes risk than does ART

.... but less than does obesity

Rotger CID 2010
Diabetes risk in HIV+ according to genetic background

In a study with 600 subjects 
→ you can assess the quantitative effect of common SNPs confirmed in GWAS 
→ but you cannot discover new SNPs

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This study: n=94 white SHCS participants with new onset diabetes 2000-2009, n=550 SHCS controls without diabetes

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→ but you cannot discover new SNPs

Rotger CID 2010
Genetic markers of HIV-related Lipoatrophy

Before ART

Subcutaneous Fat Loss

After d4T/AZT
**Genetic markers of HIV-related Lipoatrophy**

**Before ART**

- **TNF -238G>A**

- **APOC3**
  - Tarr JID 2005, Zanone Poma (ICONA) AIDS 2008

- **Mitochondrial DNA Haplogroups**

- **Hemochromatosis Gene Variants**
  - Zanone Poma (ICONA) AIDS 2008

- **FAS**
  - Zanone Poma AIDS 2008

**After d4T/AZT**

- **HLA B*4001**
  - (Thailand, d4T)
  - Wangsomboonsiri CID 2010

- **ARβ2**
  - Zanone Poma (ICONA) AIDS 2008

**Mitochondrial DNA insertions, deletions, point mutations:**

- Shikuma AIDS 2001 (Yes)
- White AIDS 2001 (Yes)
- Vittecoq JAIDS 2002 (Yes)
- Walker JAIDS 2002 (Yes)
- McComsey AIDS 2002, JAIDS 2005 (No)
- Martin AJHG 2003 (Yes)
- Ortiz JID 2011 (No)
- Morse JID 2012 (No)
Limitations of previous studies:

- Small study populations
- Phenotype definition is a +++ challenge
  - lipoatrophy, mixed lipoatrophy/lipohypertrophy
  - physician disagreement in mild cases common
  - Radiological (DXA) confirmation of fat loss not always done
- Toxic effect of d4T might overwhelm genetic factors
  - difficult to find SHCS participants on d4T who did not develop lipoatrophy
Are most mitochondrial genetic studies false positive?

1) skeptical of metabolic phenotypes associated with mitochondrial DNA “mutations” and “haplogroups”: These tend to be common variants that are evolutionarily linked and thus extremely **population-specific** → team up with an mtDNA expert
Are most mitochondrial genetic studies false positive?

1) Skeptical of metabolic phenotypes associated with mitochondrial DNA “mutations” and “haplogroups”: Most are common variants that are evolutionarily linked and thus extremely population-specific

→ team up with an mtDNA expert

No Longitudinal Mitochondrial DNA Sequence Changes in HIV-infected Individuals With and Without Lipoatrophy

Millán Ortiz,1,2* Estella S. Poloni,3,2* Hansjakob Furrer,5 Helen Kovari,6 Raquel Martinez,1 Mireia Arnedo,1,11 Luigia Elzi,7 Enos Bernasconi,9 Pietro Vernazza,10 Bernard Hirschel,4 Matthias Cavassini,2 Bruno Ledergerber,6 Huldrych F. Günthard,6 Amalio Telenti,1 Philip E. Tarr,8 and the Swiss HIV Cohort Study
Are most mitochondrial genetic studies false positive?

2) The large, well-conducted studies tend to have negative results
Are most mitochondrial genetic studies false positive?

2) The large, well-conducted studies tend to have negative results.

Comprehensive Association Testing of Common Mitochondrial DNA Variation in Metabolic Disease

Richa Saxena, Paul I. W. de Bakker, Karyn Singer, Vamsi Mootha, Noël Burtt, Joel N. Hirschhorn, Daniel Gaudet, Bo Isomaa, Mark J. Daly, Leif Groop, Kristin G. Ardlie, and David Altshuler

- 3,304 diabetics and 3,304 matched nondiabetic individuals.

- other metabolic traits (body mass index, measures of insulin secretion and action, blood pressure, and cholesterol)

“.... We did not find a significant association of common mtDNA variants with these metabolic phenotypes”
Are most mitochondrial genetic studies false positive?

2) The large, well-conducted studies tend to have negative results.

“.... European mtDNA haplogroups are unlikely to play a major role in the risk of developing the disorder.”
Are most mitochondrial genetic studies false positive?

2) The large, well-conducted studies tend to have negative results

Frailty and mortality are not influenced by mitochondrial DNA haplotypes in the very old

Joanna Collerton\textsuperscript{a}, Deepthi Ashok\textsuperscript{b}, Carmen Martin-Ruiz\textsuperscript{a}, Angela Pyle\textsuperscript{b}, Gavin Hudson\textsuperscript{b}, Mohammad Yadegarfar\textsuperscript{a}, Karen Davies\textsuperscript{a}, Carol Jagger\textsuperscript{a}, Thomas von Zglinicki\textsuperscript{a}, Thomas B.L. Kirkwood\textsuperscript{a}, Patrick F. Chinnery\textsuperscript{b,*}

\textsuperscript{a} Institute for Ageing and Health, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne NE4 5PL, UK
\textsuperscript{b} Wellcome Trust Centre for Mitochondrial Research, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne NE1 4LP, UK

- applied both Fried Frailty status and Rockwood frailty index (results similar)
- 700 over 85 year-old participants of Newcastle 85+ study

“\textit{there is currently no compelling link between inherited mtDNA variants and aging.”}
Aging and comorbidities in the Swiss HIV Cohort Study

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1) Comparison with HIV-negative population
Obesity rates are increasing in SHCS participants

Population Trends 2000-2012:
- median BMI 22.6 → 23.9
- median age 39 → 47
- On cART 85% → 97%
- Earlier ART start
- Fewer AIDS events
- Fewer IVDU

- Similar to trends in general population
- Improved health of HIV+ persons, compared to 10 years ago

With successful modern ART regimens (no AZT, no d4T) + aging HIV+ population → focus has shifted from study of lipoatrophy to the problem of obesity
Obesity rates are increasing in SHCS participants.
Abdominal obesity rates are increasing in SHCS participants
Abdominal obesity rates are increasing in SHCS participants

Iff, Hasse, Ledergerber, Tarr, manuscript in preparation
SHCS Project 627 “Fatgen”
Genetic and non-genetic factors that contribute to BMI and waist circumference change after ART begin

5,415 SHCS participants
Start of a first PI- or NNRTI-based regimen after 1.1.1998

3,814 Participants excluded
1,158 with less than 730 days of follow up
1,408 without start BMI at 0 years (+120/-120 days) from starting ART
31 without available CD4 at ART start (+120/-30 days)
150 without Middle BMI at 1 years (+120/-120 days) from starting ART
409 without end BMI at 4 years (+548/-365 days) from starting ART
353 without continuous treatment (max 62 days of interruption)
48 active intravenous drug use
257 AIDS/cancer or pregnancy in period

1,601 SHCS participants
Limitation to MSM and Heterosexual males and females
Results

SHCS Project 627 “Fatgen”

N=1601
Median age at ART start: 40 y (IQR, 34-47)
80% white, 11% black, 9% other
Nadir CD4 217 (IQR, 131-289)

Before ART to 1 year after ART initiation
• Interval between BMI determinations: mean 1.0 years (0.4-1.5)
• BMI change per year (kg/m2), mean: 0.9

1 year to 4 years after ART initiation
• Interval between BMI determinations: mean 2.9 years (1.7 – 4.2)
• BMI change per year (kg/m2), mean: 0.1
### SHCS Project 627 “Fatgen”

#### Results

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Baseline into one year of ART</th>
<th>One to four years into ART</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient (95% CI)</td>
<td>Coefficient (95% CI)</td>
</tr>
<tr>
<td>Multivariable models</td>
<td>P-value</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>Risky groups</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Heterosexual males</td>
<td>0.20 (-0.22 - 0.42)</td>
<td>0.02 (-0.06 - 0.10)</td>
</tr>
<tr>
<td>Heterosexual females</td>
<td>0.51 (-0.20 - 0.30)</td>
<td>-0.03 (-0.12 - 0.06)</td>
</tr>
<tr>
<td>Age per 10 years</td>
<td>0.15 (0.06-0.24)</td>
<td>0.02 (-0.01-0.06)</td>
</tr>
</tbody>
</table>

Iff, Hasse, Ledergerber, Tarr, manuscript in preparation
**Results**

**SHCS Project 627**

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<td><strong>Multivariable models (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>white</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>black</td>
<td>-0.04 (-0.35 - 0.27)</td>
<td>0.797</td>
</tr>
<tr>
<td>other</td>
<td>-0.56 (-0.88 - -0.24)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>CD4 groups</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-99 cells/μl</td>
<td>1.62 (1.33 – 1.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>100-199 cells/μl</td>
<td>0.44 (0.18 - 0.71)</td>
<td>0.001</td>
</tr>
<tr>
<td>200 - 349 cells/μl</td>
<td>-0.03 (-0.24 - 0.18)</td>
<td>0.791</td>
</tr>
<tr>
<td>&gt;350 cells/μl</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
## Results

**SHCS Project 627**

<table>
<thead>
<tr>
<th>Prescribed regimens</th>
<th>Multivariable models</th>
<th>Coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF, xTC, EFV</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABC, xTC, EFV</td>
<td>-0.20 (-0.24 - 0.64)</td>
<td>0.371</td>
<td></td>
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<tr>
<td>ABC, xTC, LPV</td>
<td>0.21 (-0.31 - 0.72)</td>
<td>0.437</td>
<td></td>
</tr>
<tr>
<td>ABC, 3 TC, ATV, RTV</td>
<td>0.17 (-0.43 - 0.77)</td>
<td>0.581</td>
<td></td>
</tr>
<tr>
<td>AZT, xTC, EFV</td>
<td>-0.13 (-0.45 - 0.19)</td>
<td>0.438</td>
<td></td>
</tr>
<tr>
<td>AZT, xTC, LPV</td>
<td>0.29 (-0.04 - 0.61)</td>
<td>0.087</td>
<td></td>
</tr>
<tr>
<td>AZT, xTC, NFV</td>
<td>-0.11 (-0.61 - 0.39)</td>
<td>0.671</td>
<td></td>
</tr>
<tr>
<td>TDF, xTC, LPV</td>
<td>0.29 (-0.04 - 0.62)</td>
<td>0.082</td>
<td></td>
</tr>
<tr>
<td>TDF, xTC, NVP</td>
<td>0.05 (-0.43 - 0.52)</td>
<td>0.846</td>
<td></td>
</tr>
<tr>
<td>TDF, xTC, ATV, RTV</td>
<td>0.12 (-0.19 - 0.44)</td>
<td>0.887</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.14 (-0.12 - 0.40)</td>
<td>0.296</td>
<td></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Coefficient</th>
<th>P-value</th>
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<tr>
<td>-0.16 (-0.29 - -0.04)</td>
<td>0.009</td>
</tr>
<tr>
<td>-0.14 (-0.28 - 0.00)</td>
<td>0.053</td>
</tr>
<tr>
<td>-0.24 (-0.45 - -0.03)</td>
<td>0.028</td>
</tr>
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</table>

Iff, Hasse, Ledergerber, Tarr, manuscript in preparation
Genetics of obesity in the general population

32 SNPs known to be associated with BMI in GWAS in the general population

Genetics of obesity in the general population

✔ 32 SNPs known to be associated with BMI in GWAS in the general population

SHCS 627 Cross-sectional phenotype
→ Does genetic background contribute to BMI and waist circumference?

SHCS 627 Longitudinal phenotype
→ Does genetic background contribute to BMI and waist circumference change after ART initiation?
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SNPs that contribute to osteoporosis in the general population

All these SNPs individually have small effect sizes

These SNPs contribute differently to different phenotypes

- Fracture Risk: 14 SNPs
- Bone mineral density: 56 SNPs
  - lumbar spine
  - femoral neck

Estrada Nature Genetics 2012: Meta-analysis of 17 GWAS, n= 32961 probands
Bone Mineral Density according to Genetic Score

Estrada Nature Genetics 2012
9% of population had a **56% increased** osteoporosis odds ratio, compared to intermediate genetic risk category.

9% of population had a **62% reduced** osteoporosis odds ratio.

Estrada Nature Genetics 2012
Bone Mineral Density according to Genetic Score

Odds ratio for *Fracture* according to Genetic Score

- 56%

+ 60%

← Favorable → Unfavorable

← Favorable → Unfavorable
Low trauma fractures in the SHCS:

*SHCS project 657 Osteogen*

Junier Rotger Fellay Tarr, unpublished
**Event Checking Chart: Low trauma fracture**

<table>
<thead>
<tr>
<th>Name of centre</th>
<th>SHCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient ID code</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Year of birth</td>
<td></td>
</tr>
<tr>
<td>Date of event (dd/mm/yyyy)</td>
<td></td>
</tr>
</tbody>
</table>

1. According to the definition mentioned below, has a low trauma fracture, been confirmed?

- Yes → fill in body site of fracture, date, potential secondary conditions
- No → that's all

**Definition of low trauma fracture (all 4 conditions must apply):**
- A fracture that
  1. resulted from fall from standing height or less,
  2. at walking speed or less,
  3. without additional trauma/impact (i.e. a fracture while riding bicycle, during sports, falling down stairway is NOT low-trauma),
  4. at age ≥18

- **Body Site:** e.g. right hip (femoral neck), vertebral column/single site, Vertebral column/multiple sites, right wrist (Distal radius), etc.

- If the date of the fracture is unknown, indicate the date when fracture was detected by imaging (X ray, MRI or CT)

Acknowledgment: Jennifer Hoy, Monash University
Low trauma fractures in the SHCS:

*SHCS project 657 Osteogen*

N=132 patients with a first low trauma fracture, validated by the treating physician
Low trauma fractures in the SHCS:

*SHCS project 657 Osteogen*

Non-genetic multivariable model

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<tr>
<td>Age (per year)</td>
<td>1.03</td>
<td>1.01 – 1.05</td>
</tr>
<tr>
<td>Non-caucasian</td>
<td>0.20</td>
<td>0.06 – 0.48</td>
</tr>
<tr>
<td>Past smoking</td>
<td>0.68</td>
<td>0.36 – 1.25</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.77</td>
<td>0.41 – 1.45</td>
</tr>
<tr>
<td>Packyears (per year)</td>
<td>1.01</td>
<td>0.99 – 1.03</td>
</tr>
<tr>
<td>BMI (per unit increase)</td>
<td>1.01</td>
<td>0.96 – 1.06</td>
</tr>
<tr>
<td>HCV seropositive</td>
<td>0.95</td>
<td>0.56 – 1.59</td>
</tr>
<tr>
<td>IVDU</td>
<td>1.88</td>
<td>1.11 – 3.18</td>
</tr>
<tr>
<td>CD4 Nadir</td>
<td>0.99</td>
<td>0.99 – 0.99</td>
</tr>
<tr>
<td>Tenofovir (per year)</td>
<td>1.08</td>
<td>1.01 – 1.15</td>
</tr>
<tr>
<td>PI +/- RTV (per year)</td>
<td>1.08</td>
<td>1.01 – 1.14</td>
</tr>
<tr>
<td>Parent hip fracture</td>
<td>2.86</td>
<td>1.85 – 4.31</td>
</tr>
<tr>
<td>Corticosteroids 6 mo</td>
<td>3.55</td>
<td>1.95 – 6.10</td>
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The effect of drugs per year seems to be larger than the effect of age

Junier Rotger Fellay Tarr, unpublished
Low trauma fractures in the SHCS:

SHCS project 657 Osteogen

Non-genetic multivariable model

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Corticosteroids 6 mo

Parent hip fracture 2.86 1.85 – 4.31

Fracture Endpoint

→ Does genetic background contribute to low trauma fractures?

Bone mineral density endpoint

→ Does genetic background contribute to BMD decline in patients on ART (patients with >2 DXAs, at least 2 years apart)

We’re in the process of setting up an international consortium to combine databases (patients with fractures, controls, sequential DXAs)

Junier Rotger Fellay Tarr, unpublished
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Higher prevalence of polypathology among HIV+ vs. HIV-negative persons?

Possible contributing factors:
- treatment toxicity
- co-infections hepatitis B, C
- More alcohol
- More drug use
- More smoking
- ...

Metabolic clinic at Modena University, 2002-2009
- 2854 HIV+ carefully and comprehensively studied „referral patients“
- 8562 HIV-negative persons from a „general population database“

Guaraldi CID 2011, Editorial Capeau CID 2011
Comparison Swiss HIV Cohort Study vs. CoLaus Cohort  

**CoLaus**
- Prospective study
- Population based
- Caucasian inhabitants of city of Lausanne, 35-75 years old
  - Why? Goal of study: genetic prediction via GWAS of cardiovascular disease (financed by GSK)

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*The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome*

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Firmann
BMC Cardiovasc Disord 2008
CoLaus Cohort

Lausanne population aged 35-75 years
n=56,694

Initial random sample
n=19,830 (35.0%)

54 ineligible

Contacted
n=19,776 (99.7%)

4,667 no response

Responders
n=15,109 (76.4%)

799 ineligible

6,189 refusals

Eligible for interview
n=8,121 (41.0%)

1,383 not included

Completed interview
n=6,738 (33.0%)

Non Caucasian Cohort
n=549 (8.1%)

1 withdrawal

CoLaus Study cohort
n=6,188 (91.9%)

Figure 1
Flow chart of the CoLaus Study.
CoLaus Cohort: 6188 persons, comprehensively assessed with history, physical, anthropometric, multiple questionnaires, EKG, lab testing, GWAS, stored samples

Table 3: Clinical characteristics of the participants in the CoLaus study, by gender.

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 6,188)</th>
<th>Women (n = 3,251)</th>
<th>Men (n = 2,937)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.1 ± 10.8</td>
<td>53.5 ± 10.7</td>
<td>52.6 ± 10.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.88 ± 0.08</td>
<td>0.83 ± 0.07</td>
<td>0.93 ± 0.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8 ± 4.6</td>
<td>25.1 ± 4.9</td>
<td>26.6 ± 4.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>29.3 ± 9.0</td>
<td>34.4 ± 8.2</td>
<td>23.8 ± 6.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>128 ± 18</td>
<td>125 ± 18</td>
<td>132 ± 17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>79 ± 11</td>
<td>78 ± 11</td>
<td>81 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.59 ± 1.04</td>
<td>5.61 ± 1.03</td>
<td>5.56 ± 1.04</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.63 ± 0.44</td>
<td>1.81 ± 0.43</td>
<td>1.44 ± 0.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.40 ± 1.18</td>
<td>1.16 ± 0.66</td>
<td>1.66 ± 1.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol particle size (nm)</td>
<td>272 ± 4</td>
<td>273 ± 4</td>
<td>271 ± 5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apolipoprotein B (mg/dL)</td>
<td>1.74 ± 1.34</td>
<td>1.69 ± 1.29</td>
<td>1.80 ± 1.38</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.55 ± 1.15</td>
<td>5.34 ± 1.02</td>
<td>5.78 ± 1.23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>8.44 ± 6.3</td>
<td>7.97 ± 5.47</td>
<td>9.62 ± 6.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adiponectin (µg/mL)</td>
<td>9.94 ± 8.12</td>
<td>12.32 ± 9.33</td>
<td>7.32 ± 5.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>13.1 ± 10.7</td>
<td>16.9 ± 11.7</td>
<td>8.65 ± 7.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Homocystein (µmol/L)</td>
<td>10.4 ± 4.4</td>
<td>9.4 ± 3.2</td>
<td>11.4 ± 5.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>2.49 ± 3.48</td>
<td>2.65 ± 3.71</td>
<td>2.30 ± 3.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pro-BNP (ng/L)</td>
<td>682 ± 531</td>
<td>679 ± 519</td>
<td>686 ± 545</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD. BMI: body mass index; HDL: high density lipoprotein, hsCRP: high sensitivity C-reactive protein, BNP: brain natriuretic peptide. Statistical analysis between gender by Student’s t-test or chi-square test.

Firmann BMC Cardiovasc Disord 2008
Aims of this study

SHCS project 716 (Barbara Hasse, Philip Tarr, Bruno Ledergerber)

To compare HIV- and HIV+ persons from CoLaus and the Swiss HIV Cohort Study, with regards to

- **Prevalence** of multimorbidity, comorbidity and polypharmacy

- **Incidence** and type of non-AIDS conditions
Comparison Swiss HIV Cohort Study vs. CoLaus Cohort  

_Inclusion SHCS:_ Age >35, no matching  
_Exclusions (SHCS/CoLaus):_ non-white, IVDU  
_Exclusions CoLaus:_ no follow-up visit  

**Prevalence** of comorbidities/comedication

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*CoLaus1 = Cross-sectional assessment at baseline, 2003-2006*  
*CoLaus2 = Cross-sectional assessment at baseline, 2008-2012*
Comorbidity and comedication

Comorbidities:
• Arterial hypertension (>140 mmHg systolic or >90 diastolic)
• Stroke
• Myocardial infarction
• Diabetes mellitus

Comedications:
• Antihypertensives
• Lipid lowering agents
• Platelet aggregation inhibitors
• Antidiabetics

Multimorbidity
≥2 of the above mentioned conditions (i.e. ≥2 comorbidities), in addition to HIV

Multipharmacy
≥2 medications, in addition to antiretrovirals  

SHCS project 716
Hasse Tarr Ledergerber, unpublished
Data analyses

- Descriptive analyses of baseline characteristics

- Unadjusted overall prevalence of endpoints for SHCS and CoLaus

- Risk factors:
  - Sex
  - Age 40-49, 50-64, 65+ years,
  - BMI < 18.5, 18.5-24.9, 25.0-29.9, 30+ kg/m2
  - Smoking

- Standardized predictions of prevalence (man, 50-64 year old, normal weight, smoking) for SHCS and CoLaus based on multivariable logistic regression analyses to quantify associations of available risk factors with endpoints

*SHCS project 716

slide courtesy Barbara Hasse*
## Baseline characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>SHCS</th>
<th>CoLaus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td>3284 (100)</td>
<td>4569 (100)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>616 (18.8)</td>
<td>2,450 (53.6)</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>49 (44-57)</td>
<td>57 (49-67)</td>
</tr>
<tr>
<td>BMI, median (IQR)</td>
<td>24 (22-26)</td>
<td>26 (23-29)</td>
</tr>
<tr>
<td>Ever smoker, n (%)</td>
<td>2,137 (65.1)</td>
<td>2,690 (58.9)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>1,200 (36.5)</td>
<td>971 (21.3)</td>
</tr>
<tr>
<td>PI exposure, years, median (IQR)</td>
<td>4.17 (0.85-8.19)</td>
<td>-</td>
</tr>
<tr>
<td>NNRTI exposure years, median (IQR)</td>
<td>2.24 (0-5.99)</td>
<td>-</td>
</tr>
<tr>
<td>HIV years, median (IQR)</td>
<td>1.35 (0.87-1.84)</td>
<td>-</td>
</tr>
</tbody>
</table>

*SHCS project 716*  
*slide courtesy Barbara Hasse*
Age and gender distribution

SHCS 09-11 (N=3284)

COLAUS 09-11 (N=4569)

SHCS project 716
slide courtesy Barbara Hasse
Comorbidities – observed prevalence

Myocardial infarction
Diabetes mellitus
Stroke
Hypertension
Multimorbidity

Myocardial infarction
Diabetes mellitus
Stroke
Hypertension
Multimorbidity

Prevalence % (95% C.I.)

- Myocardial infarction
- Diabetes mellitus
- Stroke
- Hypertension
- Multimorbidity

Observed prevalence
- SHCS (blue squares)
- CoLaus (red circles)

SHCS project 716
slide courtesy Barbara Hasse
Co-Medications – observed prevalence

- Antihypertensives
- Lipid lowering agents
- Antidiabetics
- Platelet aggregation inhibitors
- Multipharmacy

**Observed prevalence**
- SHCS
- CoLaus

SHCS project 716
slide courtesy Barbara Hasse
Predicted prevalence from multivariable logistic regression adjusted for age, BMI and smoking for a 50-65 year old, normal weight, male smoker

SHCS project 716

slide courtesy Barbara Hasse
Predicted prevalence from multivariable logistic regression adjusted for age, BMI and smoking for a 50-65 year old, normal weight, male smoker
Discussion

Unadjusted analyses of observed prevalences
• Comparisons are biased due to different population characteristics

Adjusted analyses
• When compared to HIV-negative persons in CoLaus, we find no evidence for increased prevalence of comorbid conditions among HIV positive individuals in the SHCS with the exception of hypertension
• Evidence of more comediations in the SHCS for all drug categories resulting in significantly increased polypharmacy in the SHCS compared to CoLaus

SHCS project 716
slide courtesy Barbara Hasse
...available results similar to „ideal“AGEhIV

Figure 1: Prevalence of the different comorbidities

SHCS

Arterial hypertension 45.3%

Diabetes mellitus 4.7%
Myocardial infarction 5.1%
Stroke 1.8%

289 HIV+ and 246 HIV -; median age 52 years

Schouten J et al. Abstract 16_39; HIV Drug Therapy, Glasgow 2012;
Peter Reiss, AG EhIV Cohort, Amsterdam, Netherlands

slide courtesy Barbara Hasse
SHCS vs. CoLaus comparison: Limitations and opportunities

- Incidence analyses (comorbidities/comedications) ongoing
- Preliminary comparison of BMI trajectories SHCS (year 1-4 of ART) vs. CoLaus over 3 years: **not** increased in SHCS
- Very few non-caucasians in CoLaus
- Very few IVDU in CoLaus
  - We are in the process of getting IVDU + hepatitis C data from CoLaus
- CoLaus focus is on CV disease: Limited spectrum of comorbidities available for analyses such as liver disease, kidney disease, malignancies, lung and bone disease
- Grant for a 3rd wave of cross-sectional CoLaus assessments has been submitted
- Opportunities for further collaborative/comparative studies in future
Summary

• Increasing opportunities to apply «general population» genomics data to aging-related conditions in HIV+ persons

• Consider jointly all relevant factors, not just genetic background and evaluate their effect sizes
  • Traditional risk factors (for osteoporosis, coronary disease, ...)
  • HIV-related factors (immune suppression, ...)
  • ART-related factors (current or duration of exposure to specific drugs)
  • Genetic background
Summary

- Results from our collaboration with CoLaus study is only a first step – we need further in-depth analyses of these and other HIV+ vs. HIV-negative populations.

- Will do our best to get frailty measurements introduced in the Swiss HIV Cohort Study.

- Will be interested in doing genetic study including mitochondrial DNA sequencing, looking for association with frailty phenotypes.
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CoLaus: Gerard Waeber, Peter Vollenweider, Vincent Mooser, Pedro Marques-Vidal,

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