Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse

# Developing an analysis plan

Tracy Glass

# Conflicts of Interest

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I have received funding for membership on Data Safety and Monitoring Boards and for the preparation of educational materials from:

Gilead Sciences

Novartis

Janssen-Cilag

# Outline

Swiss TPH

A real-life example:

1. The idea
2. Which data to use and which data to be careful about
3. What to do about personal and sensitive data
4. Are the data we need available?
5. Refining the research question
6. Consideration of biases and limitations

The stages of an analysis plan

# The idea

A doctor involved in the Swiss HIV Cohort Study (SHCS) approached me about answering the following quesiton:

*In the era of 'test and treat', how will a patient's symptom status when starting ART impact their clinical outcomes?*

Hypothesis: individuals starting ART when they feel well, may not be ready to start ART and therefore will have more problems with adherence and therefore be at risk for worse clinical outcomes.

Can we answer this question with data from the SHCS?

# The idea

***Q:*** *how will a patient's symptom status when starting ART impact their clinical outcomes?*

**Population**

People living with HIV initiating antiretroviral therapy for the first time

**Exposure ('Intervention'/Comparator group)**

**I =** People starting ART with a no symptoms

**C =** People starting ART without symptoms

**Outcomes**

Adherence

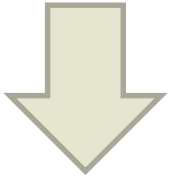
Viral failure

Resistance

# Which data to use?

- Swiss HIV Cohort Study is a **cohort study** which collates data on people living with HIV aged over 16 years who have accessed care in one of the collaborating centres in the UK, at any time in 1996 or thereafter.

- **Data** are those collected in **routine** HIV clinical care (*CD4 counts, HIV viral load, ART, basic demographics)*



1. is it safe to use this data?
2. Pragmatically can I answer this research question?
3. what are the potential limitations of these data?

# 2 - Which data do I need to be careful about?

**a) Personal data**: "*data which relate to a living individual who can be identified*

*(a) from those data, or*

*(b) from those data and other information which is in the possession of, or is likely to come into the possession of, the data controller* "

Examples: Name, Clinic/hospital name, Address, Postal/zip code, Date of birth

# 2 - Which data do I need to be careful about?

**b) Sensitive data**: "*Data consisting of information relating to: racial or ethnic origin, political opinions, religious beliefs, membership of a trade union, physical or mental health, sexual life, criminal offences*"

Examples: Ethnicity, Religion, Sexuality, HIV-positive status, Salary, Bank account number

# 3 – What to do about personal and sensitive data?

Want to collect as much personal/sensitive information as you need to conduct your study but not collect and hold unnecessary data

Collecting personal and sensitive data will require informed consent and ethical approval.

e.g. location

Address → postcode → region → urban/rural → ??

# 3 – What to do about personal and sensitive data? (2)

In the SHCS, consent given to collect and utilize data for research – do not need to get consent for individual projects with no additional data collection.

Need to check local policies and procedures for obtaining ethical approval before proceeding

After data collection:

- Need to be careful when publishing the data to ensure anonymity – follow data protection guidelines
- Many journals require data to be made publicly available which raises privacy concerns if data not properly anonymized.

Source: https://www.dataprotection.ie/docs/Anonymisation-and-pseudonymisation/1594.htm

# 4- Are the data we need available?

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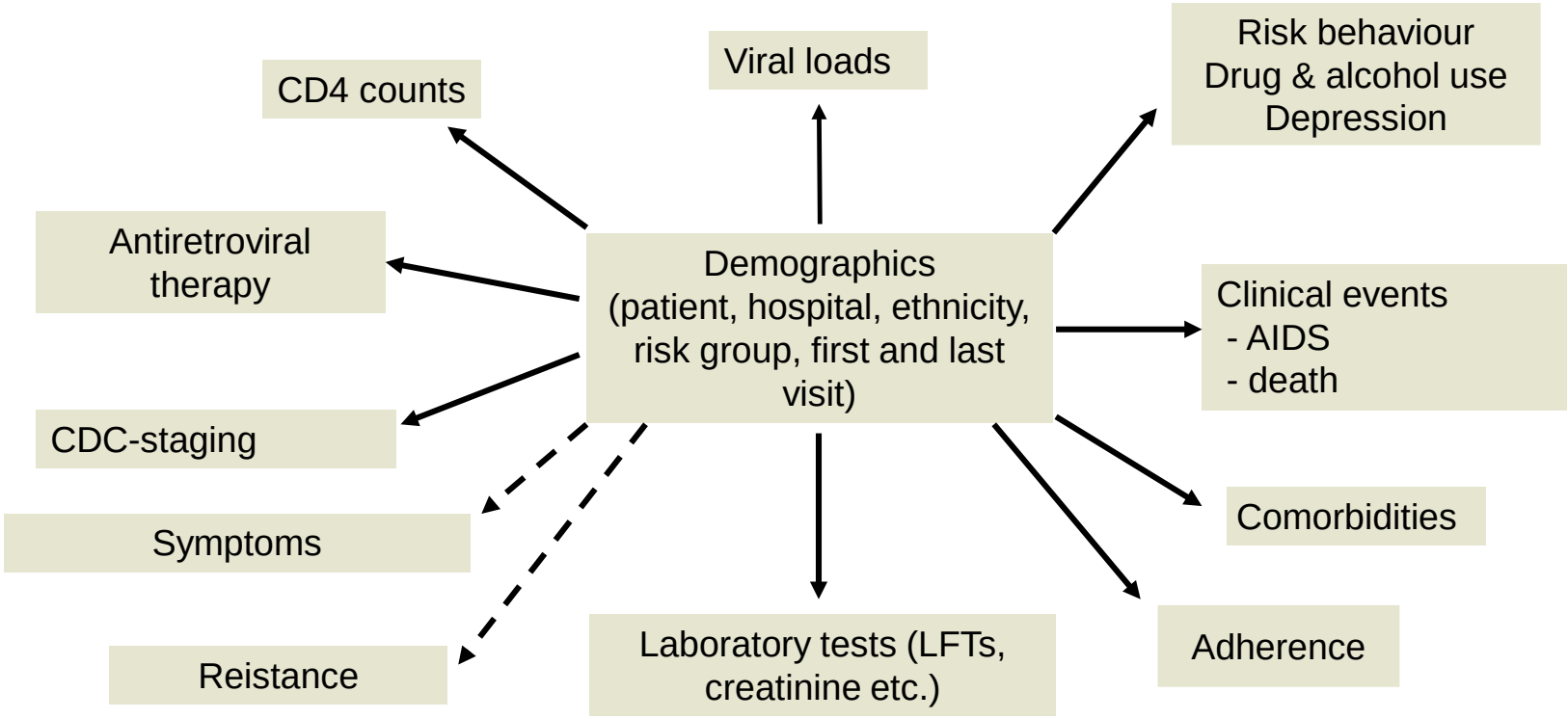
Question: *how will a patient's symptom status when starting ART impact their clinical outcomes (adherence, viral failure, resistance)?*



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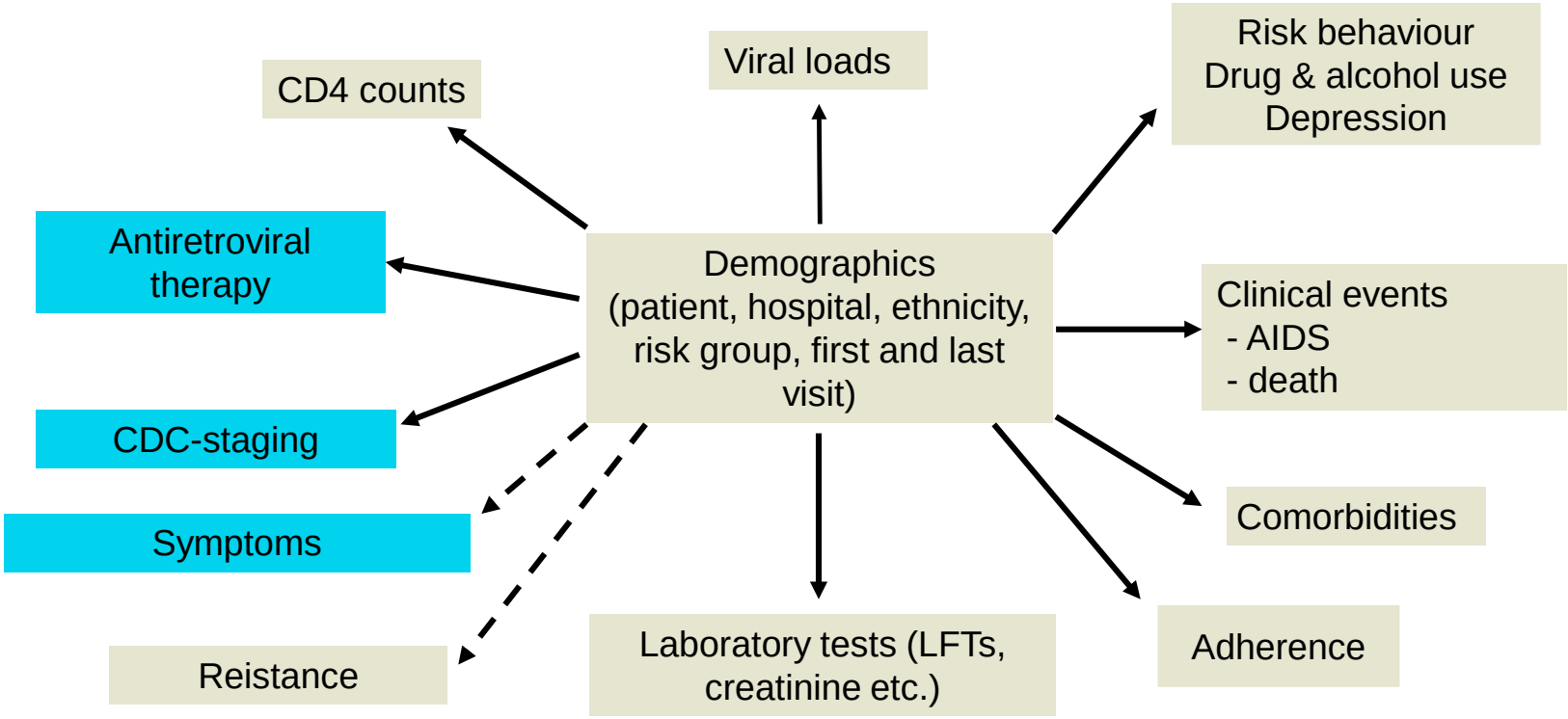
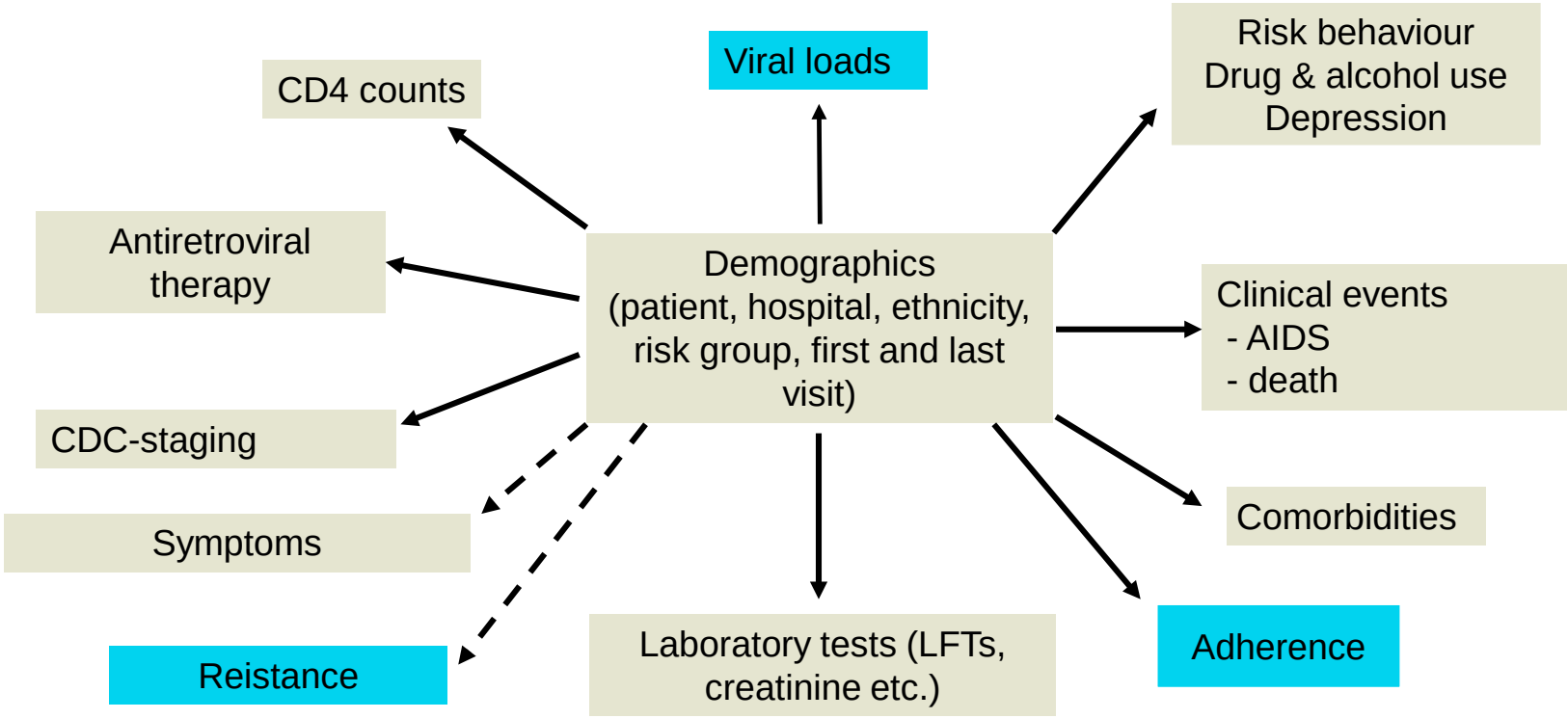


# 4- Are the data we need available?

Swiss TPH

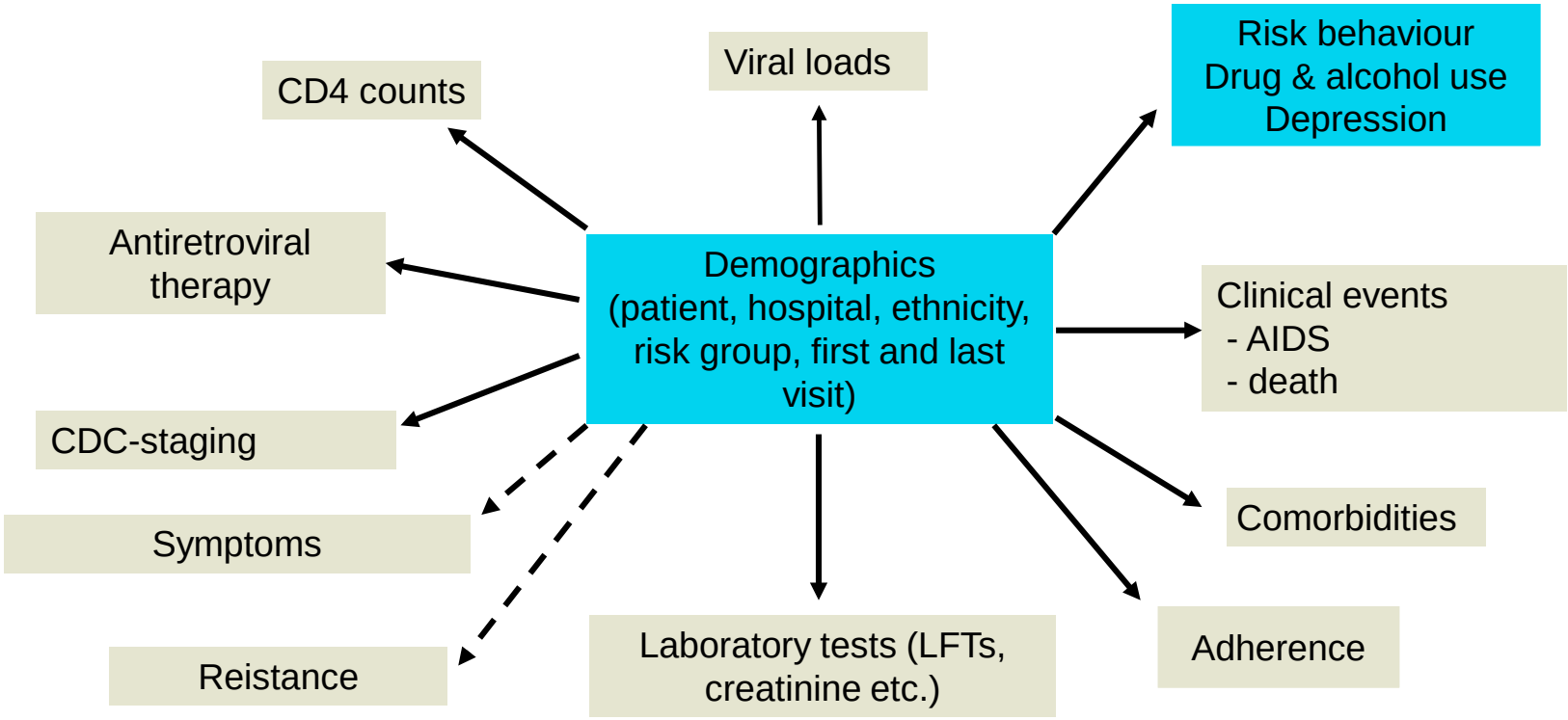
Question: *how will a patient's symptom status when starting ART impact their clinical outcomes (adherence, viral failure, resistance)?*



# 4- Are the data we need available?

Swiss TPH

Question: *how will a patient's symptom status when starting ART impact their clinical outcomes (adherence, viral failure, resistance)?*



# 5- Refining the research question

**Q:** *how will a patient's symptom status when starting ART impact their clinical outcomes?*

## Population

HIV-positive adults initiating ART for first time

Also need to have symptom status, adherence, and viral loads

Exclusion criteria:

- Pregnancy
- ART started before 2003

# 5- Refining the research question

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## How do we measure exposure?

What constitutes 'asymptomatic'?

## Exposure

**I :** People starting ART with CDC-stage A

**C :** People starting ART with CDC-stage B or C

# 5- Refining the research question

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## How do we measure outcome?

What constitutes non-adherence?

2 question asked by clinician:

1) Have you missed a dose of ART in the last 4 weeks?

   Never
   Once every 4 weeks
   Once every 2 weeks
   Once a week
   More than once a week
   Every day

2) Have you missed more than one dose in a row in 24 hours?

Measured twice yearly (minimum)

# 5- Refining the research question

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## How do we measure outcome?

What constitutes viral failure?

- RNA >50? >200? >400 copies/ml?
- Confirmed/unconfirmed?
- In what time frame?

# 5- Refining the research question

## How do we measure outcome?

What constitutes resistance?

- New mutations? Measured only in those with viral failure – assume all others have no resistance?
- Implies baseline resistance is measured
- In what time frame?

# 5- Refining the research question

**Q:** *how will a patient's symptom status when starting ART impact their clinical outcomes?*

**Hypotheses:**

Patients starting ART when asymptomatic are more likely to:

1) Missed any doses of ART
2) Time to viral failure (two consecutive RNA>50 copies/ml)
3) Development of new resistance mutation

# 6 – What biases do we need to consider

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## Confounding

1. Before the guidelines were changed, who would have started ART when asymptomatic (i.e., CDC stage A)?

2. Do you think these people would differ from those starting with symptoms? How?

3. Have these data been collected (so that we can adjust for these factors)?

# 6 – What biases do we need to consider

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| | Symptomatic | Asymptomatic | Total |
|---|---|---|---|
| | N=1862 | N=5269 | N=7131 |
| Age (years), median (IQR) | 41 (33-50) | 37 (30-45) | 38 (31-46) |
| Male Gender | 1322 (71%) | 4156 (79%) | 5478 (77%) |
| Caucasian | 1324 (71%) | 3841 (73%) | 5165 (73%) |
| Education < 9 years | 497 (27%) | 1121 (21%) | 1618 (23%) |
| Risk group for HIV infection | | | |
| Men having sex with men | 643 (37%) | 2974 (59%) | 3617 (53%) |
| Heterosexual | 933 (53%) | 1739 (34%) | 2672 (39%) |
| IV drug | 133 (8%) | 296 (6%) | 429 (6%) |
| Other | 51 (3%) | 65 (1%) | 116 (2%) |
| Unsafe sexual behavior* | | | |
| No partner/safe sex | 1508 (85%) | 3745 (75%) | 5253 (77%) |
| Reported unsafe sex | 238 (13%) | 1133 (23%) | 1371 (20%) |
| Refused to answer | 6 (0%) | 31 (1%) | 37 (1%) |
| Unknown/missing | 27 (2%) | 102 (2%) | 129 (2%) |

# 6 – What biases do we need to consider

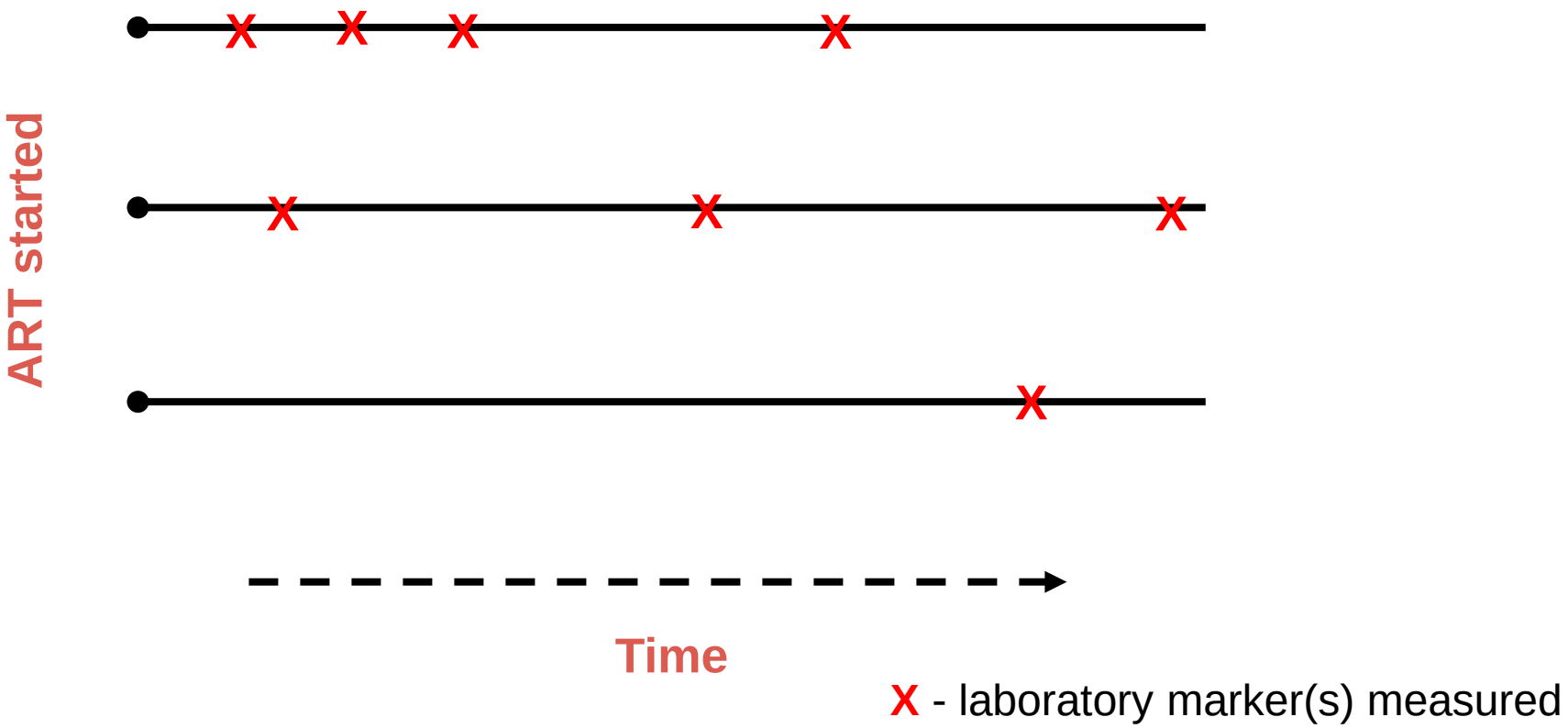
## Missing data

- Who might not have CDC-stage measured at baseline?
- Who might not have a viral load measured?

## Infrequent monitoring

- Why might some have more follow-up visits than others (and therefore more adherence and viral loads measurements)?

# 6 – What biases do we need to consider



# Outline

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The stages of an analysis plan

# Before you write the analysis plan

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## 1. Feasibility analysis

- Need to have enough people starting ART while asymptomatic
- Patients need to have:

  -adherence questionnaire

  -laboratory measures available

  -resistance test results available at ART start and virological failure
- Will our sample size be large enough?
- Will we observe enough outcome events?

# Before you write the analysis plan

## 2. Write the concept sheet

About 1-2 pages

- Title
- Hypothesis/background
- Aim(s)
- Inclusion/exclusion
- Proposed analysis in brief
- Variables needed
- Possible limitations

# Analysis Plan

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Research question and choice of exposure and outcome variables will determine most appropriate statistical tests/models to use

Should be outlined in concept sheet

Sensitivity and sub-group analyses may be needed – should be planned a priori

***But . . . .***

May have to be more flexible than in RCTs

As project develops, analysis plan may change

# Analysis Plan

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## Descriptive analyses

- Get to know your data!
- Identify differences in exposure groups and potential confounders

## Main analysis

- Analysis of primary endpoint
- Adjusting for confounders (regression models)

## Exploratory/sub-group analyses

- Not your main endpoint
- Provide some insight/aids interpretation of main results

## Sensitivity analyses

- Are methods and definitions valid?

# Descriptive analyses

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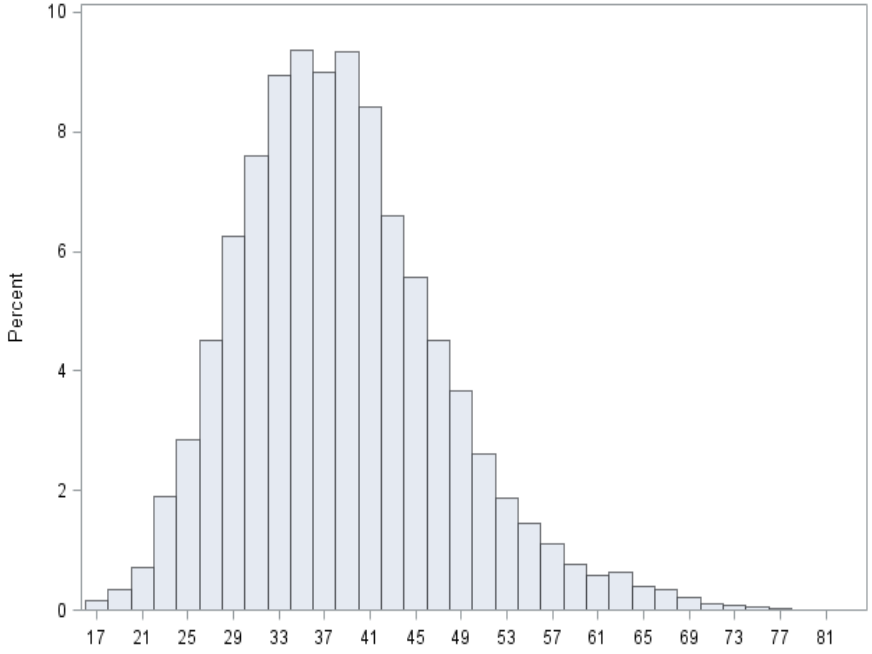
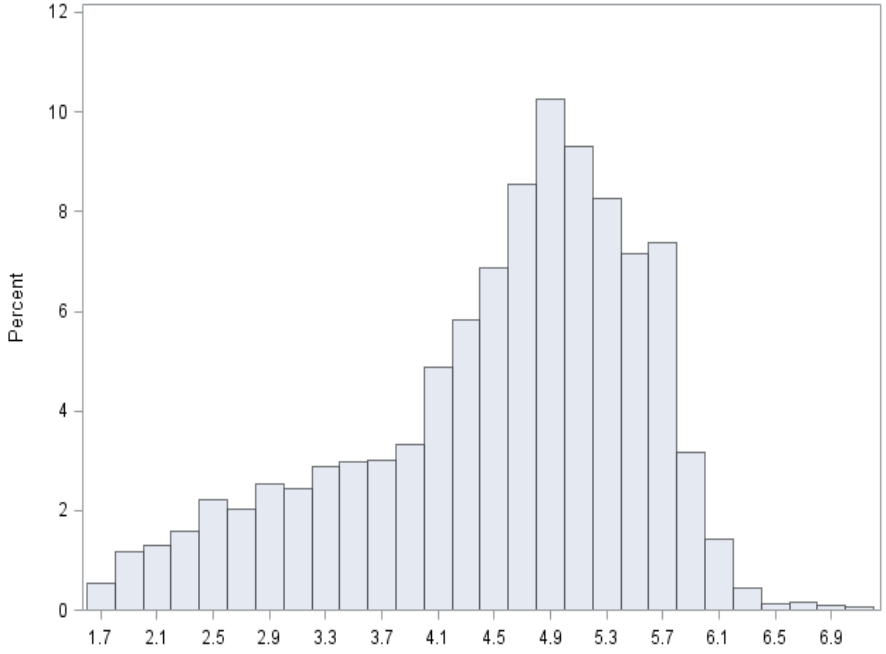
1. Data checks
2. Patient flow through study
3. Number of people with and without exposure of interest
4. Describe baseline demographic and clinical characteristics according to exposure of interest
5. Patient follow-up
6. Outcome

# Descriptive analyses

1) Data checks (errors, outliers, normal distribution, missing data etc.)




**Age at ART start**




**$Log_{10}$ VL at ART start**

# Descriptive analyses

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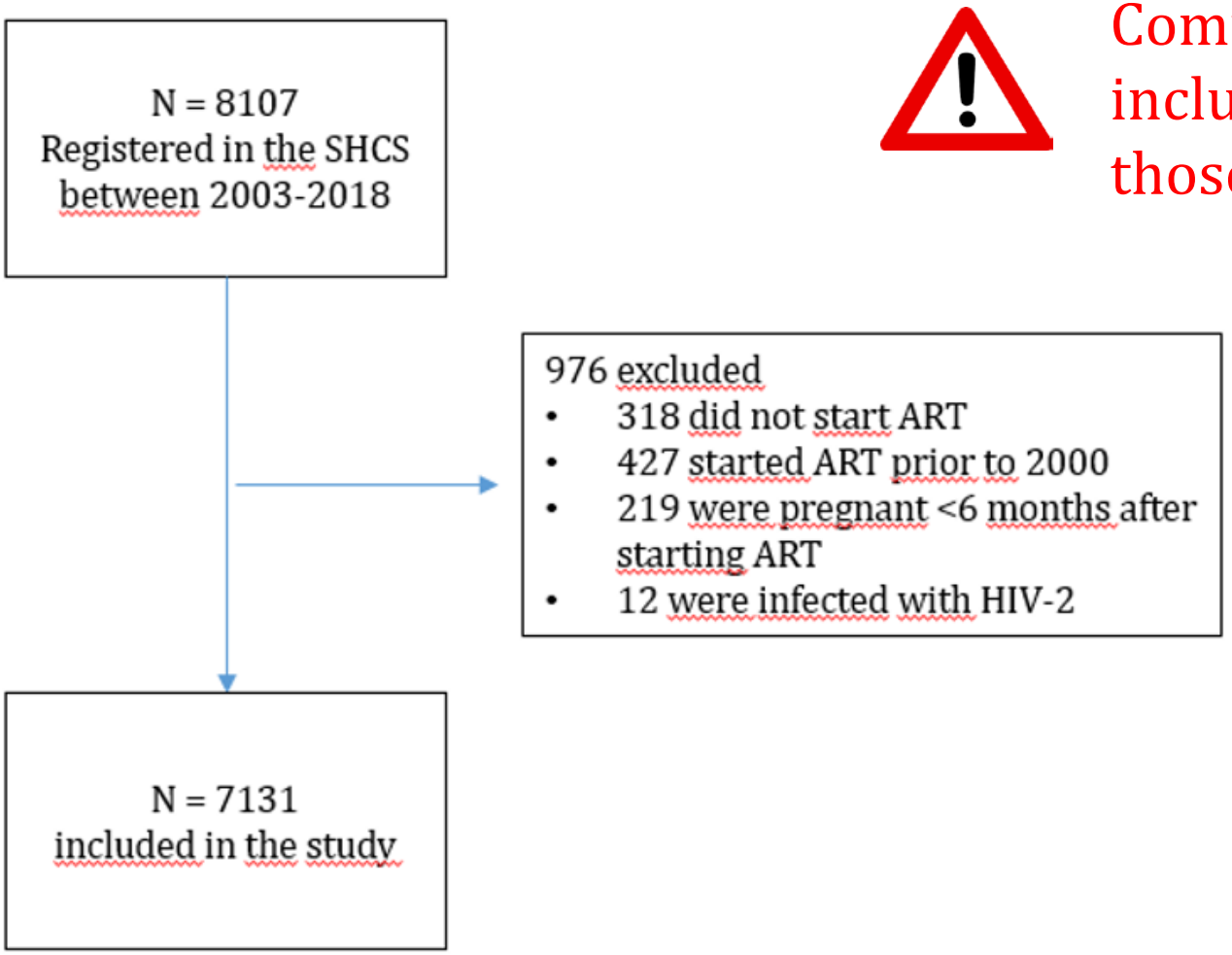
## 2) Patient flow






Compare those included from those excluded

# Descriptive analyses

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## 3) Number of people with and without exposure of interest

Those with CDC-stage A within 30 days of starting ART

## 4) Other characteristics of the sample

- Demographics, HIV markers, AIDS events, cART regimen, calendar year, HBV/HCV co-infection etc.
- Summarize by exposure of interest (asymptomatic status)

# Descriptive analyses

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| | Symptomatic | Asymptomatic | Total |
|---|---|---|---|
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| Age (years), median (IQR) | 41 (33-50) | 37 (30-45) | 38 (31-46) |
| Male Gender | 1322 (71%) | 4156 (79%) | 5478 (77%) |
| Caucasian | 1324 (71%) | 3841 (73%) | 5165 (73%) |
| Education < 9 years | 497 (27%) | 1121 (21%) | 1618 (23%) |
| Living alone* | 680 (38%) | 1965 (39%) | 2645 (39%) |
| Receiving psychological treatment* | 214 (12%) | 704 (14%) | 918 (14%) |
| Legal problems (including imprisonment)* | 20 (1%) | 89 (2%) | 109 (2%) |
| Initial ART regimen | | | |
| NNRTI | 707 (38%) | 1979 (38%) | 2686 (38%) |
| non-boosted PI | 904 (49%) | 2093 (40%) | 2997 (42%) |
| boosted PI | 202 (11%) | 1037 (20%) | 1239 (17%) |
| Integrase inhibitors | 0 (0%) | 1 (0%) | 1 (0%) |
| Triple nucleoside/FI/Other | 49 (3%) | 159 (3%) | 208 (3%) |
| CD4 count (cells/mmol), median (IQR) | 123 (36-269) | 318 (217-459) | 279 (156-420) |
| CD4 count stratum (cells/mmol) | | | |
| <200 | 1060 (64%) | 920 (21%) | 1980 (33%) |

# Descriptive analyses

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## 5) Patient follow-up

- Time under follow-up
- Frequency of monitoring (laboratory tests, resistance tests)
- Comparison by exposure of interest (asymptomatic status)

| | Symptomatic | Asymptomatic | Total |
|---|---|---|---|
| | N=1862 | N=5269 | N=7131 |
| Years on ART | 8.1 (3.8-11.6) | 6.4 (3.2-9.8) | 6.8 (3.3-10.3) |
| ***Adherence*** | | | |
| Number of adherence questionnaires, median (IQR) | 17 (8 – 26) | 12 (6 – 21) | 13 (6 – 13) |

# Descriptive analyses

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## 6) Outcome

- Percentage with non-adherence (at what time point?)
- Crude rate of virological failure
- Comparison by exposure of interest

| | Symptomatic | Asymptomatic | Total |
|---|---|---|---|
| | N=1862 | N=5269 | N=7131 |
| Worst reported missed doses, year 1 (%) | | | |
| 0 missed doses | 1205 (82%) | 3196 (82%) | 4401 (82%) |
| 1 missed dose | 161 (11%) | 456 (12%) | 617 (12%) |
| 2 missed doses | 49 (3%) | 112 (3%) | 161 (3%) |
| >2 missed doses | 52 (4%) | 116 (3%) | 168 (3%) |
| HIV-1 RNA ≥ 50 copies/µl (N=6747) | | | |
| Viral rebound [b] | 954 (54%) | 1957 (39%) | 2911 (43%) |
| Confirmed viral rebound [c] | 484 (27%) | 994 (20%) | 1478 (22%) |
| Weeks to confirmed viral rebound | 93 (50-218) | 103 (61-217) | 99 (57-217) |

# Descriptive analyses

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## 6) Outcome

- Number of resistance mutations at viral failure

| | Symptomatic | Asymptomatic | Total |
|---|---|---|---|
| | N=1862 | N=5269 | N=7131 |
| ***Resistance*** | | | |
| Transmitted resistance, % (N=5073) | 180 (13%) | 460 (12%) | 640 (13%) |
| NRTI | 70 (5%) | 170 (5%) | 240 (5%) |
| NNRTI | 108 (8%) | 251 (7%) | 359 (7%) |
| PI | 43 (3%) | 98 (3%) | 141 (3%) |
| Integrase inhibitors | 0 (0%) | 1 (0%) | 1 (0%) |
| Newly acquired resistance, % (N=1025) | 90 (27%) | 95 (14%) | 185 (18%) |
| NRTI | 75 (31%) | 67 (17%) | 142 (22%) |
| NNRTI | 55 (23%) | 59 (15%) | 114 (18%) |
| PI | 10 (4%) | 10 (3%) | 20 (3%) |
| Integrase inhibitors | 2 (7%) | 2 (6%) | 4 (6%) |

# Main analyses

- Should answer research question
- Provide estimates that are adjusted for measured confounders (regression models)
- Potential confounders:
  - ART regimen
  - Demographics (sex, ethnicity, education)
  - Status of HIV partner, sexual risk behavior

**Table A2:** Generalized estimating equation models for factors associated with self-reported non-adherence to ART

| Variable | Univariable | Multivariable | p-value |
|---|---|---|---|
| Asymptomatic when starting ART | 1.03 (0.93-1.15) | 1.03 (0.93-1.15) | 0.576 |

# Sensitivity analyses

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If we change variable definitions, do our conclusions remain unchanged?

How do we define virological failure?

Cutoff for viral load?

**Table A3:** Cox proportional hazards model for time to confirmed viral rebound

| Variable | RNA>50 copies/mL | p-value | RNA>200 copies/mL | p-value |
|---|---|---|---|---|
| Asymptomatic when starting ART | 0.83 (0.72 – 0.95) | 0.008 | 1.11 (0.92 – 1.33) | 0.272 |

# Sensitivity analyses

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If we change the time frame of the study, do our conclusions remain unchanged?

Are people starting ART in 2003 have the same probability of success of treatment than those starting in 2017?

Are HIV-infected individuals the same (demographically) in 2003 than in 2017?

In sensitivity analyses considering the subset of individuals starting ART from 2010 onwards, the association was even stronger (HR 0.59, 95% CI: 0.45-0.76, p<0.001).

# Exploratory analysis

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Aware of large limitation - reasons for starting ART when asymptomatic is not known

Undertook range of preliminary analyses to understand differences between the exposure groups

- Predictors of starting ART when asymptomatic

- Changes in asymptomatic status at ART start over time (i.e., before and after guidelines)

# Write and publish the paper

Swiss TPH

**The role of asymptomatic status when starting AR**

**treatment outcomes and the implications for test-**

**HIV Cohort Study**


Tracy R. Glass[1,2], Huldrych Günthard[3,4], Alexandra Calmy[5], Enos
Scherrer[7], Manuel Battegay[2,8], Ana Steffen[9], Jürg Böni[4], Sabine
Matthieu Perreau[12], Matthias Cavassini[13], Hansjakob Furrer[14] a
Study

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**Adherence in patients who are asymptomatic at the time of starting antiretroviral therapy**

Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse
Associated Institute of the University of Basel


Tracy R. Glass[1,2], Manuel Battegay[2,3], Matthias Cavassini[4], Alexandra Calmy[5], Enos Bernasconi[6], Patrick Schmid[7], Huldrych Günthard[8], and Hansjakob Furrer[9,10] on behalf of the Swiss HIV Cohort Study

[1] Swiss Tropical & Public Health Institute, Basel, Switzerland; 2) University of Basel, Basel, Switzerland; 3) University Hospital Basel, Basel, Switzerland; 4) University Hospital Lausanne, Lausanne, Switzerland; 5) University Hospital Geneva, Geneva, Switzerland; 6) Ospedale Civico Lugano, Lugano, Switzerland; 7) Kantonsspital St. Gallen, St. Gallen, Switzerland; 8) University Hospital Zurich, Zurich, Switzerland; 9) Bern University Hospital, Bern, Switzerland; 10) University of Bern, Bern, Switzerland.


**Background:**

- With the advent of a 'test-treat' approach recommended by the WHO in September 2015, a significantly higher share of HIV-infected individuals will be starting ART when asymptomatic.
- Starting ART at an asymptomatic stage with higher CD4 counts has been shown to be a risk-factor for non-adherence, treatment interruptions, and unsuppressed viral load [1].
- The aim of this study was to compare adherence patterns and clinical outcomes in naïve patients starting ART according to symptom status.

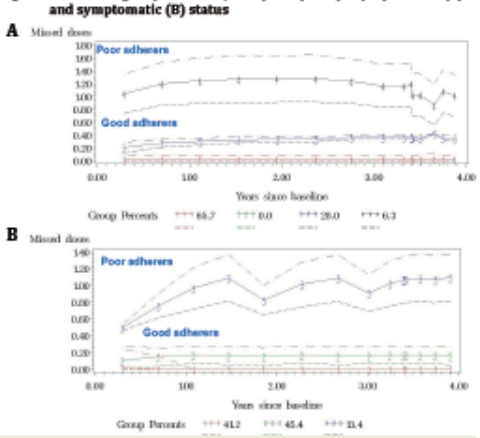
**Methods:**

- All ART-naive patients aged ≥18 years who were not pregnant, started ART between 2003 and 2015, followed for ≥1 year and completed ≥1 adherence questionnaire were included
- Asymptomatic was defined as CDC-stage A prior to starting ART
- Self-reported missed doses in the last 4 weeks was recorded at clinical visits (daily, more than once a week, once a week, once every second week, once a month, never).
- Viral failure: RNA viral load>500 copies/ml after > 24 weeks on ART.
- Cox proportional hazard models were used to assess the association between symptom status and viral rebound.
- Group-based trajectory analysis to explore trends and patterns in self-reported adherence. Similar to latent class analysis, trajectory modeling assumes that the population is composed of a mixture of distinct groups defined by their behavioral trajectories.

**Table: Pre-ART characteristics by asymptomatic status**

| | Total | Asymptomatic | Symptomatic |
|---|---|---|---|
| | 3539 (100%) | 2546 (72.4%) | 973 (27.6%) |
| Male Gender, n (%) | 2960 (76.7) | 1996 (70.4) | 702 (72.2) |
| Age, median (IQR) | 39 (32–47) | 38 (32–45) | 41 (35–49) |
| Caucasian, n (%) | 2895 (79.7) | 2015 (79.2) | 790 (81.2) |
| Basic education*, n(%) | 738 (21.2) | 506 (20.0) | 232 (24.4) |
| Stable partner, n(%) | | | |
| No partner | 700 (38.9) | 558 (38.6) | 222 (39.6) |
| HIV-positive | 356 (17.7) | 277 (19.4) | 79 (14.1) |
| HIV-negative | 603 (30.0) | 431 (29.8) | 172 (30.7) |
| Unknown status | 268 (13.4) | 181 (12.5) | 87 (15.5) |
| Imported sexual sex, n(*) | 456 (22.6) | 353 (24.3) | 103 (18.3) |
| CD4 cell count (cells/mm³) | | | |
| Median (IQR) | 279 (186 – 387) | 301 (218 – 415) | 200 (70 – 317) |
| <350 | 2321 (68.0) | 1556 (63.3) | 765 (80.4) |
| <9 years of schooling | | | |

**Figure: Adherence groups from trajectory analysis by asymptomatic (A) and symptomatic (B) status**




**Results:**

- Asymptomatic patients did not differ significantly to symptomatic patients with respect to reported adherence (p=0.18) or treatment interruptions (p=0.33) in year 1.
- Asymptomatic status was significantly associated with a reduced risk of viral rebound (HR: 0.71, 95% CI: 0.60-0.84) but not after adjusting for year of starting ART (HR: 0.89, 95% CI: 0.75-1.05).
- Similar patterns in adherence across symptom status were identified by trajectory analysis (Figure) with a clear group of 'poor adherers' being identified. However, asymptomatic patients were less often put into the 'poor' adherence group (6.3% vs. 13.4%).
- Being in the poor adherence group was significantly associated with poor clinical outcomes :
  - Poor adherers were more likely to experience treatment interruptions (3.3% vs. 1.5%, p=0.007) and viral rebound (13.2% vs. 5.2%, p<0.001) within 1 year after starting ART.
- Baseline characteristics and symptom status prior to starting ART predicted membership in the poor adherence group.

**Conclusions:**

# Summary

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It is possible to answer a research question using data from your own clinic and without the need for big program grants

Need to be aware of potential biases and limitations that are present

Lots of background work/analyses that don't make it to the finished article

Get statistical advice from the start!