HIV Medicine

Caroline Sabin
University College London, UK
HIV Medicine Workshop

Caroline Sabin
Conflict of Interest

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

- Gilead Sciences
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- Merck Sharp & Dohme

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Reviewing papers: what to look for in Real World Evidence (RWE) studies

Caroline A. Sabin
Editor-in-Chief, HIV Medicine
Reviewing papers: what to look for in Real World Evidence (RWE) studies

Caroline A. Sabin

Editor-in-Chief, HIV Medicine

- Are they really ‘real-world’?
- Do they provide strong evidence?
Real World Evidence (RWE) – my reaction
RWE studies, PubMed, 1984-2023
RWE and Pharma
Plan of talk

• How do we ‘assess’ whether a new drug intervention works?
• What is RWE?
• What should you look for when reviewing RWE studies?
Assessing whether a new drug intervention works

Does a new drug work in an ideal setting and for ‘ideal’ people?
Assessing whether a new drug intervention works

Does a new drug work in an ideal setting and for ‘ideal’ people?

• Test of **efficacy**
• Generally studied in RCT
Parallel design RCTs

Randomisation

New intervention

Control group

Compare treatment groups

Starting point

Present time

Follow individuals
Other features of RCTs

• Usually fairly strict inclusion/exclusion criteria – population restricted to those most likely to benefit and/or complete trial

• Close attention to uptake of intervention – treatment switches generally ignored (intent-to-treat analysis)

• Regular monitoring of participants

• Losses-to-follow-up recorded and incorporated into analyses appropriately
Assessing whether a new drug intervention works

Does a new drug work in an ideal setting and for ‘ideal’ people?

- Test of **efficacy**
- Generally studied in RCT
- Highly selected population
- High fidelity to intervention
- High *internal* validity but *external* validity uncertain

Do we really believe we will see the same treatment effect if the drug is given to a different population with different characteristics?
Assessing whether a new drug intervention works

Does a new drug work in an ideal setting and for ‘ideal’ people?

Does a new drug work in a normal setting with ‘normal’ people?
Assessing whether a new drug intervention works

Does a new drug work in a normal setting with ‘normal’ people?

Does a new drug work in an ideal setting and for ‘ideal’ people?

- Test of **effectiveness**
- Still usually studied in RCT
- More representative population
- Realistic fidelity to intervention
- Thus higher external validity
## RCTs of efficacy vs. effectiveness

<table>
<thead>
<tr>
<th>Efficacy study</th>
<th>Effectiveness study</th>
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<tbody>
<tr>
<td><strong>Question</strong></td>
<td>Does the intervention work in real-world practice?</td>
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<tr>
<td>Does the intervention work under ideal circumstance?</td>
<td></td>
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<tr>
<td><strong>Setting</strong></td>
<td>Real-world everyday clinical setting</td>
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<tr>
<td>Resource-intensive ‘ideal setting’</td>
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<tr>
<td><strong>Study population</strong></td>
<td>Heterogeneous population Few to no exclusion criteria</td>
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<tr>
<td>Highly selected, homogenous population</td>
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<tr>
<td>Several exclusion criteria</td>
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<td><strong>Providers</strong></td>
<td>Representative usual providers</td>
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<td>Highly experienced and trained</td>
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<tr>
<td><strong>Intervention</strong></td>
<td>Applied with flexibility Concurrent interventions and cross-over permitted</td>
</tr>
<tr>
<td>Strictly enforced and standardized No concurrent interventions</td>
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Assessing whether a new drug intervention works

- Does a new drug work in an ideal setting and for ‘ideal’ people?
- Does a new drug work in a normal setting with ‘normal’ people?
- Does a new drug work in a real-world setting when not used as part of a trial?
Assessing whether a new drug intervention works

- Does a new drug work in an ideal setting and for ‘ideal’ people?

- Does a new drug work in a real-world setting when not used as part of a trial?
  - ‘Real-word’ effectiveness
  - Usually studied in cohort/registry
  - Representative population
  - Little attention on fidelity to intervention

- Does a new drug work in a normal setting with ‘normal’ people?
Cohort studies

- Disease-free
  - Exposed to factor
    - Has outcome
    - Does not have outcome
  - Not exposed to factor
    - Has outcome
    - Does not have outcome

Starting point → Present time → Follow individuals → Future time
But why rely solely on RCTs or cohorts?

• Many clinics collect information on those attending their service
• People are treated and monitored following standard protocols
• Includes those not normally be considered for inclusion in a RCT
• Why not use this information to learn about how a drug works in a fully representative and unselected, population?
“.. information on health care that is derived from multiple sources outside typical clinical research settings, including electronic health records (EHRs), claims and billing data, produce and disease registries, and data gathered through personal devices and health applications.”
Example: Real-life experience with bictegavir (BIC)/emtricitabine (FTC)/tenofovir anafenamide (TAF)

- Observational, retrospective, single-centre study in Barcelona
- All adults with HIV starting BIC/FTC/TAF from 8/6/2018
- Viral suppression (<50 copies/ml) rates (on-treatment)
  - M6: ART-naïve 77%  ART-experienced 94%
  - M12: ART-naïve 92%  ART-experienced 93%
- Suppression rates were not as high as those observed in RCTs of treatment-naïve people treated with BIC/FTC/TAF

Example: Impact of switch to DTG vs. continuation of PI/r in people at risk of prior NRTI resistance

- Quebec HIV Cohort of 10,219 people with HIV
- Inclusion: all PWH with virologic failure or exposure to mono/dual NRTI therapy who were virologically suppressed on PI/r-based regimen for >6 months (n=532)
- 216 (40.6%) changed regimen to DTG+2NRTIs; 316 (59.4%) remained on PI/r+2NRTIs
- Weighted hazard ratio for effect of DTG switch on virologic failure: 0.57 (95% CI 0.21, 1.52)

N’dongo Sangare M et al. Open For Infect Dis 2020; 7(11): ofaa404
RWE studies to investigate drug adverse events

• RCTs may be limited in their ability to detect relatively infrequent adverse events due to lack of power and/or duration of trial
• Observational/RWE datasets may offer a means to identify adverse drug events
• But results must always be interpreted with caution, particularly where adverse events are unexpected
Example: Integrase strand transfer inhibitor (INSTI) use and diabetes mellitus (DM)

- Used IBM MarketScan databases to identify PWH newly starting antiretroviral therapy (ART)
- Primary outcome: new-onset DM/hyperglycemia in 6 months after ART initiation
- INSTI use associated with increased risk of new-onset DM/ hyperglycaemia (HR 1.31 (95% CI 1.15-1.48))

O’Halloran JA et al. *Clin Infect Dis* 2022 (on-line, ahead of print)
Limitations of RWE studies

• Data are not usually collected for research purposes and there may be issues around data quality/accuracy

• Observational studies subject to many different sources of bias, including:
  – Bias resulting from confounding/channelling
  – Missing/incomplete data
  – Monitoring bias
  – Attrition bias
  – Misclassification bias
  – Survivorship bias
  – Lead-time bias
Bias due to confounding

Occurs when a spurious association arises (or is hidden) due to a failure to fully adjust for factors related to both the risk factor and outcome.
Example: is nevirapine associated with poorer virological outcomes than efavirenz?

- Several cohorts had reported that those receiving nevirapine had a poorer virological outcome than those receiving efavirenz.
- Efavirenz may cause anxiety/depression and sleep disturbances, and is not recommended for use in those with mental health problems.
- The presence of mental health problems is a known risk factor for poor drug adherence.
- At that time, few cohort studies were able to collect high quality data on prior mental health problems in their participants.
‘Channelling’ in RWE studies

ART drugs are not given randomly...

- Previous mental health conditions
- efavirenz or nevirapine?
- Viral suppression
Defining endpoints in RCTs vs RWE studies

• RCT endpoints:
  - Defined in advance
  - Capture the ‘most important’ aspects of disease progression
  - Able to discriminate between treatment arms
  - Mindful of regulatory requirements

• But in a cohort/registry, may have concerns relating to:
  - Missing data
  - Infrequent and/or irregular measurements
  - Changes in laboratory methods over time
  - Selection of patients and monitoring bias

• Intent to treat (ITT) analyses
  - What do these mean in the context of a non-randomised study?
Defining endpoints (2)

• Have to define endpoints differently

Example: HIV RNA at 48 weeks

**RCT:** HIV RNA at week 48 visit (+/- 7 days)

**Cohort/registry:** nearest HIV RNA to 48 weeks (+/- 6 weeks)

• Are these really comparable endpoints?
Example: Real-life experience with bictegravir (BIC) /emtricitabine (FTC)/tenofovir anafenamide (TAF)

- All adults receiving BIC/FTC/TAF after 8th June 2018
- Effectiveness, HIV RNA <50 copies/mL
  - On-treatment (OT): discontinuation/missing=excluded
  - Modified intention-to-treat (mITT): discontinuation=failure, missing=excluded
  - Intention-to-treat (ITT): discontinuation/missing=failure
- But what does ITT mean if there is no randomisation?
- Does missing really equal virological failure?
- Are the results really directly comparable to those from RCTs?

Example: Real-life experience with bictegravir (BIC)/emtricitabine (FTC)/tenofovir anafenamide (TAF)

Received at least one dose of BIC/FTC/TAF N=1605

Received only BIC/FTC/TAF N=1584

Baseline Cohort

Did not reach 6-month follow-up n=285

Reached M6 since BIC/FTC/TAF initiation N=1299

Cohort at 6 Months

Remained on BIC/FTC/TAF n=1148

Discontinued BIC/FTC/TAF n=151

n=213 (13%) TN

n=1371 (87%) TE

n=21

n=1137 (88%) TE

Figure 1. Flow chart of the cohort of PLWH who received at least one dose of BIC/FTC/TAF.

(c)

Suppression rates at M6

HIV–RNA <50 [cp/ml] [% Patients (95% CI)]

OT  m-ITT  ITT

94% (92%; 94%)  89% (87%; 91%)  83% (80%; 85%)

Treatment-naive PLWH

Treatment-experienced PLWH

The possibility of monitoring bias

• If you look for something more often, you’ll detect it sooner...

• Are people all monitored equally and at the same frequency?

• Examples:
  – renal function among people starting ART
  – sleep disturbances
  – monitoring of weight/BMI
  – Assessment for diabetes mellitus

• What impact does this have on reported associations with outcomes?
So can we trust the results of ALL RWE studies?

“However, the confluence of large datasets of uncertain quality and provenance, the facile analytic tools that can be used by nonexperts, and a shortage of researchers with adequate methodologic savvy could result in poorly conceived study and analytic designs that generate incorrect or unreliable conclusions.”

Are RWE studies any different to cohorts?

- No - RWE studies are observational studies with branding!
Are RWE studies any different to cohorts?

- No - RWE studies are observational studies with branding!
- Need to apply the same epidemiological rigor to them as for cohort studies
- Guidance exists.....
RWE studies are increasingly being published – evidence from these studies is often promoted with the same strength as that from RCTs. RWE studies have the potential to be of huge value for understanding how drugs work in a real-life setting when used for the treatment of people who are more representative of those seen for clinical care. Can also suggest unexpected yet important adverse events that may have been missed in RCTs. However, these studies have the potential to be affected by several major biases, and thus results should always be treated cautiously.
Summary – top tips for reviewing RWE studies

- What is the **SOURCE** of the data and what impact could this have?
  - Single clinic, multi-clinic, multi-country?
  - Electronic health record data, patient notes or specific prospective data collection?

- How are people **FOLLOWED UP**?
  - Do endpoint definitions allow for different follow-up patterns?
  - How do the authors deal with any missing outcomes?

- Are any **COMPARISONS** being made?
  - Are comparison groups similar and if not, could this introduce confounding?
  - If so, how was confounding addressed in analyses?

- Are the results **UNEXPECTED** or are they supported by other evidence?