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Inserm
La science pour la santé
From science to health

What to look for in a paper?

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Disclosures

- I have received consultancy fees, honoraria, travel grants, and my team study grants from:
  - HIV board Gilead France from 2011 until december 2015
  - Consultancy Innavirvax (2015 et 2016), Merck Switzerland (2017)
  - Lectures Janssen (2016, 2018), MSD (2015, 2017)
  - Travel/accommodations/meeting expenses ViiV(2015)
  - Grants from Janssen (2015, 2017-2018), MSD (2017), ViiV (2015)

Outline

- General principles
- A working example
- To go further

General principles

To identify

- The research question
  - Which hypothesis is being explored?
- The **study design**
  - Was the study design appropriate for the research question
- Where
    - Title, abstract, end of the introduction
- This will allow you to know what to look at
  - which will depend on the study design

To analyse the methodology I

- Study population
  - **Where were the individuals enrolled**?
  - **Inclusion and non-inclusion criteria**
  - Comparability of groups
    - Randomization if any
      - And how it was performed
- Adapted to answer the research question?
- Enough details for someone to redo the study?
- Where?
  - Mainly in the material and method section

To analyse the methodology II

- Methods
  - Definition of **endpoints** (**primary** and secondary)
  - Validity of endpoints, how and when they were measured
  - **Sample size**
    - details on sample size calculation
- Adapted to answer the research question?
- Enough details for someone to redo the study and the analysis?
- Where?
  - Mainly in the material and method section

To analyse the methodology III

- Methods
  - Duration and rhythm of follow-up
  - **Prevention and/or minimization of bias**
    - For instance, blinding for a RCT
  - **Appropriate analyses**
    - For instance ITT for a RCT
  - Ethics
- Adapted to answer the research question?
- Enough details for someone to redo the study and the analysis?
- Where?
  - Mainly in the material and method section

To criticize result presentation

- Coherence of the number of subjects in the different sections
- Appropriate follow-up (lost-to-follow-up, missing data)
- Completeness of endpoint reporting in particular effect size calculation together with precision estimate (confidence interval, …)
- Clarity of results reporting
  - Is the result reported in an interpretable way for a non specialist?
- Look at tables and figures and whether the content is coherent with the text
- Where?
  - Mainly in the result section/Abstract/Conclusion

To criticize result interpretation

- Correct interpretation of the results?
  - Statistical significance does not mean causality
- When the difference is statistically significant, is it clinically pertinent?
- Were the potential bias presented and discussed?
  - Are the study limits presented and discussed fairly
  - Can you think of potential bias that are not discussed
    - » **Useful only if likely to change the results**
- Are the results new, are they coherent with the literature?
- Are the conclusions supported by the results?
- Where?
  - Mainly in the discussion/conclusion section

Example

Newer Antiretroviral Drugs for HIV

	Dolutegravir	Elvitegravir/COBI	Rilpivirine
Study	SPRING-2, SINGLE, FLAMINGO	Study 102, 103	Echo-Thrive Study
Convenience	Small pill once-daily	Single tablet regimen	Small pill once-daily
Efficacy (HIV-RNA<50 at week 48, 96)	• **Non-inferior to RAL** (81% vs 76%) • **Superior to EFV*** (80% vs 72%) • **Superior to DRV/r** (81% vs 76%)	• **Non-inferior to EFV** (83% vs 82%) • **Non-inferior to ATV/r** (84% vs 83%)	• **Non-inferior to EFV if HIV-RNA <100,000** (84% vs 80%)
Resistance	No DTG resistance detected	2% failure with EVG/c resistance	Cross-resistance with etravirine
Toxicity	Rapid increase in serum creatinine	Rapid increase in serum creatinine	Fewer CNS AE and rash than EFV
Interactions	Few DDI	Potential DDI through COBI	Caution with PPI, H2-Blockers

*In the SINGLE trial DTG was combined only with ABC/3TC

Sax PE, et al. Lancet. 2012; Zolopa A, et al. JAIDS, 2013; Wohl D, et al. ICAAC 2013; DeJesus E, et al. Lancet. 2012; Rockstroh J, et al. JAIDS; 2013; Clumeck N, et al. EACS 2013; Cohen CJ, AIDS 2013

An example

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dolutegravir plus Abacavir–Lamivudine for the Treatment of HIV-1 Infection

Sharon L. Walmsley, M.D., Antonio Antela, M.D., Ph.D., Nathan Clumeck, M.D., Dan Duiculescu, M.D., Andrea Eberhard, M.D., Felix Gutiérrez, M.D., Laurent Hocqueloux, M.D., Franco Maggiolo, M.D., Uriel Sandkovsky, M.D., Catherine Granier, D.E.S.S., Keith Pappa, Pharm.D., Brian Wynne, M.D., Sherene Min, M.D., and Garrett Nichols, M.D., for the SINGLE Investigators*

N Engl J Med 2013;369:1807-18.

The example: Abstract 1

BACKGROUND

Dolutegravir (S/GSK1349572), a once-daily, unboosted integrase inhibitor, was recently approved in the United States for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in combination with other antiretroviral agents. Dolutegravir, in combination with abacavir–lamivudine, may provide a simplified regimen.

METHODS

We conducted a randomized, double-blind, phase 3 study involving adult participants who had not received previous therapy for HIV-1 infection and who had an HIV-1 RNA level of 1000 copies per milliliter or more. Participants were randomly assigned to dolutegravir at a dose of 50 mg plus abacavir–lamivudine once daily (DTG–ABC–3TC group) or combination therapy with efavirenz–tenofovir disoproxil fumarate (DF)–emtricitabine once daily (EFV–TDF–FTC group). The primary end point was the proportion of participants with an HIV-1 RNA level of less than 50 copies per milliliter at week 48. Secondary end points included the time to viral suppression, the change from baseline in CD4+ T-cell count, safety, and viral resistance.

The last sentence of the introduction

that are resistant to NNRTIs.[7-9] We designed Study ING114467 (SINGLE) to assess the safety and efficacy of dolutegravir at a dose of 50 mg plus a fixed-dose combination of abacavir–lamivudine, as compared with fixed-dose efavirenz–tenofovir DF–emtricitabine, which is the only single-tablet regimen currently preferred in the U.S. HIV treatment guidelines[1,2] and one of two currently recommended single-tablet regimens in the European treatment guidelines.[3]

Questions

- Can you tell
  - The research question?
  - The design?
    - RCT or Observational Study
    - The type
      - Parallel, Cross-over, Cluster
        - » Superiority, Non-inferiority
  - The study population
  - Was the study randomized?

But

STATISTICAL ANALYSIS

According to the protocol, we could conclude that treatment with dolutegravir and abacavir–lamivudine was noninferior to treatment with efavirenz–tenofovir DF–emtricitabine if the lower boundary of a two-sided 95% confidence interval for the difference in the primary end point was less than 10 percentage points lower in the DTG–ABC–3TC group than in the EFV–TDF–FTC group. This margin is consistent with that in other trials in this population.[19] Assuming a 75% response rate in the EFV–TDF–FTC group, we calculated that 394 participants who could be evaluated would need to be included in each group for the study to have 90% power to determine the noninferiority of dolutegravir and abacavir–lamivudine, at a one-sided significance level of 2.5%. Efficacy and safety analyses were performed in the intention-to-treat population and safety population, respectively; both populations included all participants who underwent randomization and received at least one dose of study drug. The two populations were identical in this study.

- So, what is the study type?
- Do we have information on sample size?
- Do we know the primary endpoint?
- The secondary endpoints?

The example: Abstract 2

RESULTS

A total of 833 participants received at least one dose of study drug. At week 48, the proportion of participants with an HIV-1 RNA level of less than 50 copies per milliliter was significantly higher in the DTG–ABC–3TC group than in the EFV–TDF–FTC group (88% vs. 81%, P=0.003), thus meeting the criterion for superiority. The DTG–ABC–3TC group had a shorter median time to viral suppression than did the EFV–TDF–FTC group (28 vs. 84 days, P<0.001), as well as greater increases in CD4+ T-cell count (267 vs. 208 per cubic millimeter, P<0.001). The proportion of participants who discontinued therapy owing to adverse events was lower in the DTG–ABC–3TC group than in the EFV–TDF–FTC group (2% vs. 10%); rash and neuropsychiatric events (including abnormal dreams, anxiety, dizziness, and somnolence) were significantly more common in the EFV–TDF–FTC group, whereas insomnia was reported more frequently in the DTG–ABC–3TC group. No participants in the DTG–ABC–3TC group had detectable antiviral resistance; one tenofovir DF–associated mutation and four efavirenz-associated mutations were detected in participants with virologic failure in the EFV–TDF–FTC group.

CONCLUSIONS

Dolutegravir plus abacavir–lamivudine had a better safety profile and was more effective through 48 weeks than the regimen with efavirenz–tenofovir DF–emtricitabine. (Funded by ViiV Healthcare; SINGLE ClinicalTrials.gov number, NCT01263015.)

Example - Results

EFFICACY

A rapid and sustained virologic response was observed, with 88% of the participants in the DTG–ABC–3TC group, as compared with 81% of those in the EFV–TDF–FTC group, having the primary end point of a plasma HIV-1 RNA level of less than 50 copies per milliliter at week 48 (Fig. 2A). The adjusted treatment difference between the two groups was 7 percentage points (95% confidence interval [CI], 2 to 12), with dolutegravir and abacavir–lamivudine meeting the noninferiority criterion. In addition, the dolutegravir and abacavir–lamivudine regimen was shown to be statistically superior to the efavirenz–tenofovir DF–emtricitabine regimen (P=0.003). Overall differences in response (intention-to-treat analysis) were due primarily to discontinuations because of adverse events (10 of 414 participants [2%] in the DTG–ABC–3TC group and 42 of 419 [10%] in the EFV–TDF–FTC group) (Table 1).

Similar results were observed in the per-protocol population, from which 2% of the participants were excluded (11 of 414 participants [3%] in the DTG–ABC–3TC group and 7 of 419 participants [2%] in the EFV–TDF–FTC group), owing to a number of reasons, including the use of prohibited medication (in <1% of participants). In this analysis, 90% of the participants in the

Do you think that the design and the results were reported fairly in the abstract?

Do we know the effect size?

A final thought

- The non inferiority limit was set to 10%
  - meaning that a maximum difference of 10% in the proportion of individuals with a viral load <50 copies/mL was considered as non inferior
- The effect size was estimated as
  - 7% (2-12)
  - Is this difference clinically important?
- Do you think that the conclusion of the abstract is fair?

To go further

PICOT

- P Population
- I Intervention
- C Comparator
- O Outcome
- T Time frame

Reporting guidelines

http://www.equator-network.org/

• Consort	RCT
• Strobe	Observational studies
• Stard	Diagnosis accuracy
• Prisma	Meta-analysis of RCT
• Moose	Meta-analysis of OS
• Cheers	Health economics
• Gather	Health estimates
• Grade	Clinical guidelines
• …	