Cohorte et essais cliniques :
complémentarité et limites dans le traitement de l'infection à VIH
Quel apport en terme de tolérance à long terme ?

Dominique **Costagliola**

U943, Inserm et Université Pierre et Marie Curie, Paris

Tolérance et essais

L’apport des essais en termes de tolérance

- Porte sur la tolérance immédiate
  - Nausées, vomissement, diarrhées, anomalies biologiques

Exemple dans un essai chez le naïf : Darunavir vs Lopinavir

Table 3. Summary of safety.

Incidence, *n* (%)	DRV/r (*n* = 343)	LPV/r (*n* = 346)
Mean treatment exposure (weeks)	95	91
Any serious AE	34 (10)	55 (16)
Any serious AE at least possibly related to PI	3 (1)	10 (3)
Any AE leading to withdrawal[a]	19 (5.5)	35 (10.1)
Grade 2–4 AEs at least possibly related to study treatment (incidence ≥2% of patients)[b]		
Any grade 2–4 AE	80 (23)	119 (34)
Gastrointestinal AE (all)	23 (7)	52 (15)
Diarrhea	14 (4)***	38 (11)
Nausea	6 (2)	10 (3)
Rash (all types)	9 (3)	5 (1)
Grade 2–4 laboratory abnormalities (incidence ≥2% of patients)		
Alanine aminotransferase	38 (11)	40 (12)
Aspartate aminotransferase	39 (11)	35 (10)
Neutrophil count	30 (9)	11 (3)
Hyperglycemia	28 (8)	26 (8)
Pancreatic amylase	25 (7)	18 (5)
Alkaline phosphatase	5 (2)	5 (2)
Partial thromboplastin time	8 (2)	9 (3)
Pancreatic lipase	8 (1)	8 (2)
Hyperbilirubinemia	4 (1)	17 (5)
Prothrombin time	2 (1)	7 (2)
Total cholesterol	60 (18)**	95 (28)
Calculated low-density lipoprotein[c]	62 (18)	50 (15)
Triglycerides	15 (4)***	46 (13)

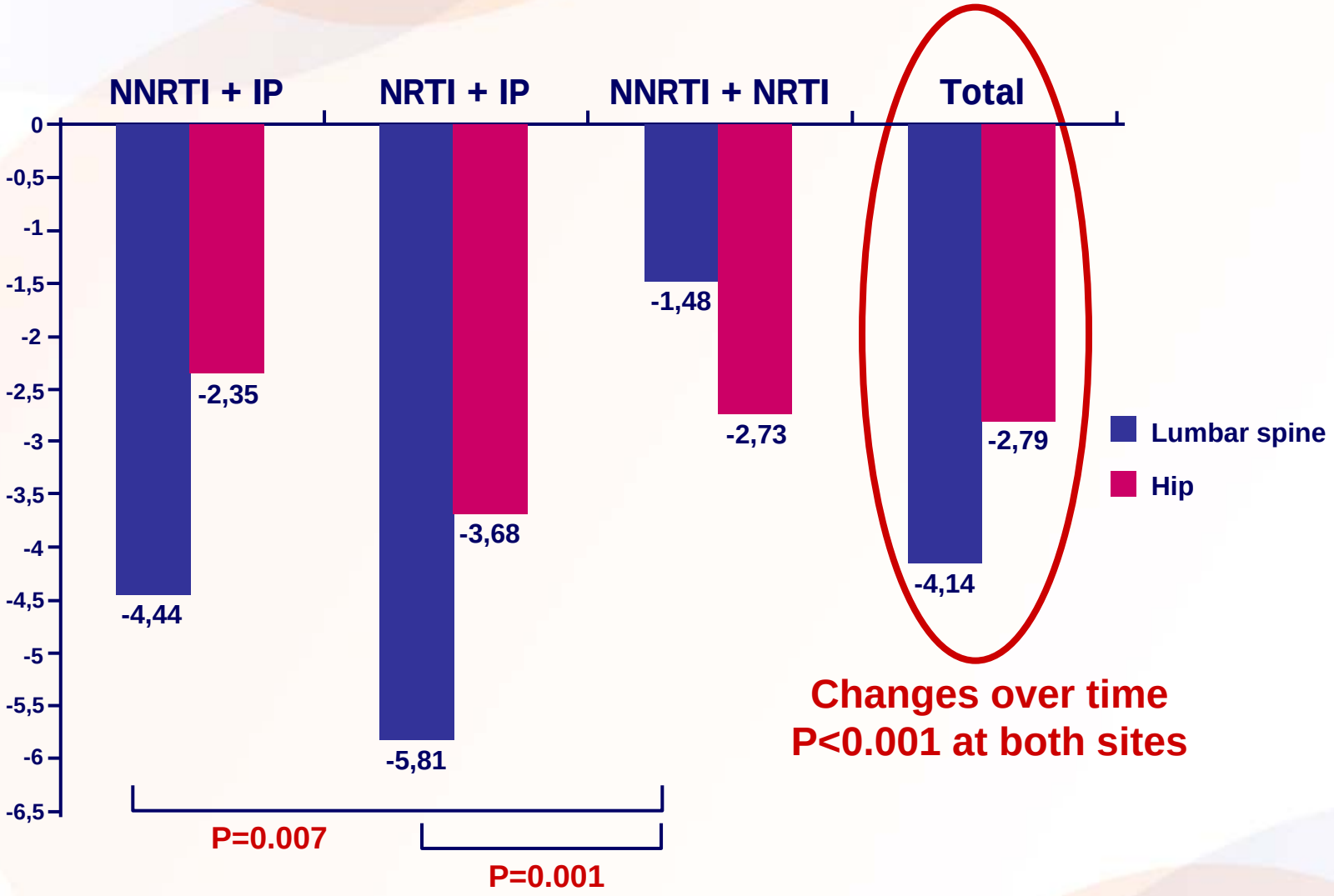
689 patients suivis 2 ans

Mills AM et al, AIDS 2009

L’apport des essais en termes de tolérance

- Porte sur la tolérance immédiate
  - Nausées, vomissement, anomalies biologiques
- Porte sur des marqueurs intermédiaires
  - Densité minérale osseuse / Fracture
  - Epaisseur intima média / Infarctus du myocarde
  - …

Evolution de la DMO Dans l'essai ANRS 121



Duvivier C et al, AIDS 2009

L’apport des essais en termes de tolérance

- Porte sur la tolérance immédiate
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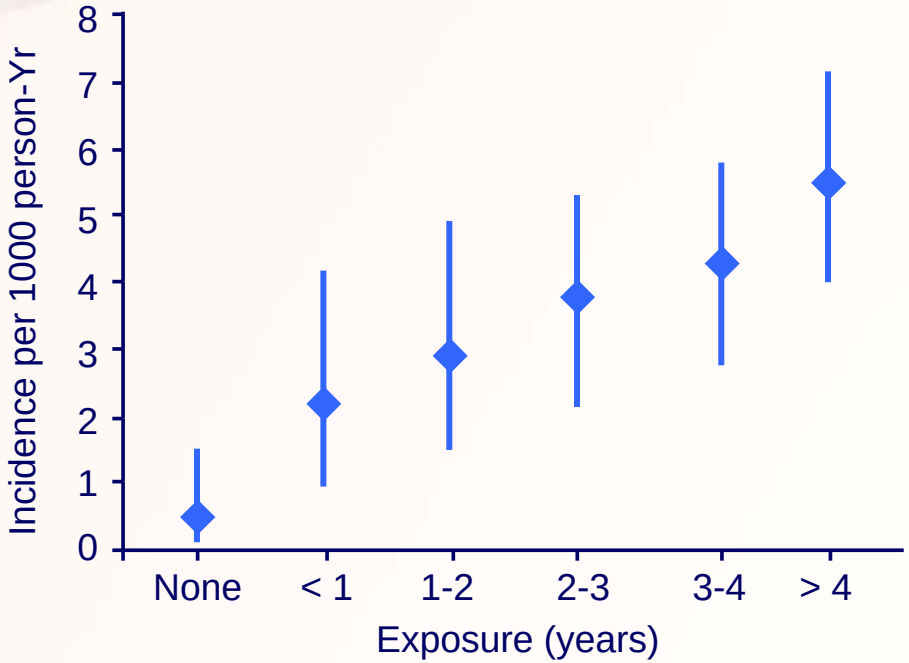
  - …
- Est limité par la puissance et la durée pour la survenue d’événements cliniques
  - Chez le patient naïf à l’heure actuelle on suit environ 600 patients pendant 2 ans
    - 1200 patients années

Combination Antiretroviral Therapy and the Risk of Myocardial Infarction

The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group*



No. of events	**3**	**9**	**14**	**22**	**31**	**47**
No. of person-years	**5714**	**4140**	**4801**	**5847**	**7220**	**8477**

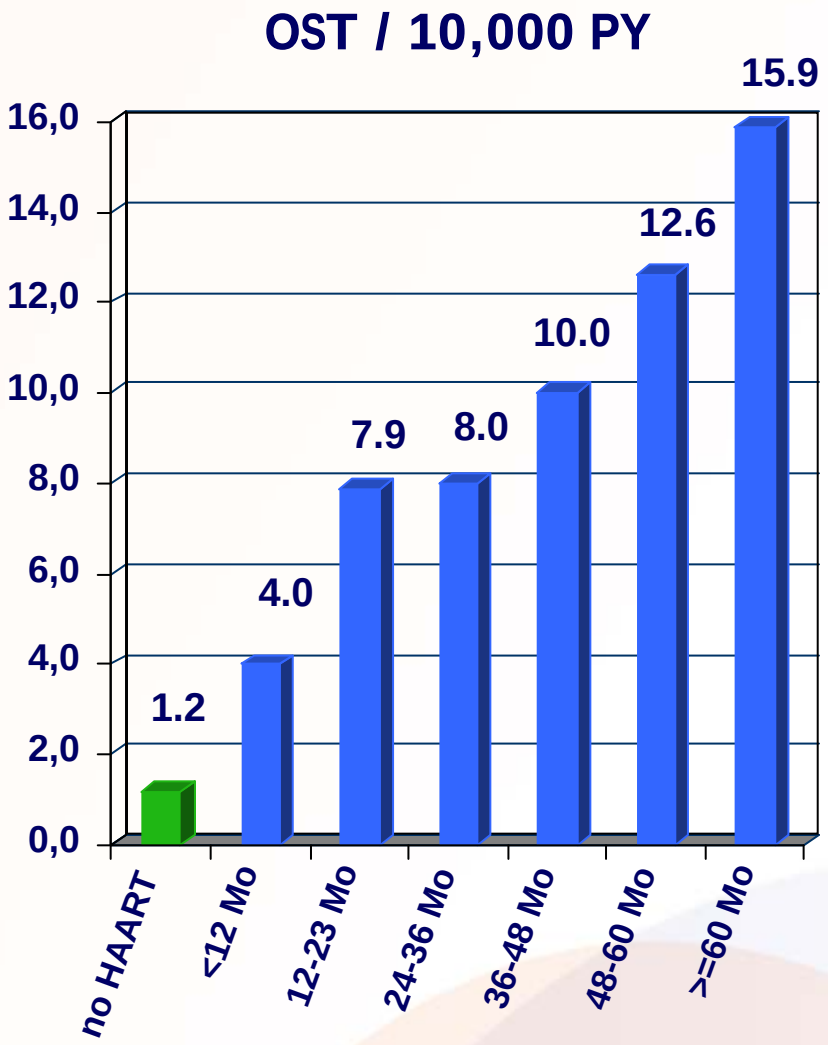
Figure 1. Incidence of Myocardial Infarction According to the Duration of Exposure to Combination Antiretroviral Therapy.

126 cas et 36 199 patients années

N Engl J Med 2003;349:1993-2003

Incidence de l'osteonécrose selon la durée d'exposition à une cART

- 104 cas chez 56 393 patients avec au moins un suivi entre 1996 et 2002 avec 229 031 patient-années de suivi (suivi moyen 4,1 années)



Mary-Krause et al, AIDS 2006

Resumé des études évaluant l'association entre l'exposition à l'abacavir et le risque d'infarctus

Study	Design	CV Events	Effect of ABC?
D:A:D[1] (N of MI = 580)	Observational cohort	Prospective, predefined	Yes
FHDH[2] (N of MI = 289)	Case control study	Prospective, MI retrospectively validated	Yes 1st yr of exposure
SMART[3] (N of MI = 19)	RCT, observational analyses	Prospective, predefined	Yes
STEAL[4] (N of MI = 3)	RCT	Prospective	Yes
GSK analysis[5] (N of MI = 11)	12 RCTs	Retrospective database search	No
ALLRT ACTG A5001[6] (N of MI = 27)	5 RCTs	Retrospective by 2 independent reviewers	No
HEAT[7] (N of MI = 0)	RCT	Prospective	No

All or majority of patients antiretroviral-experienced at ABC initiation

All or majority of patients antiretroviral naive at ABC inclusion

1. Lundgren JD, et al. CROI 2009. Abstract 44LB.
2. Lang S, et al. CROI 2009. Abstract 43LB.
3. SMART. AIDS. 2008;22:F17-F24.
4. Carr A, et al. CROI 2009. Abstract 576.
5. Cutrell A, et al. IAC 2008. Abstract WEAB0106.
6. Benson C, et al. CROI 2009. Abstract 721.
7. McComsey G, et al. 16th CROI 2009. Abstract 732.

Abacavir and the risk of heart attack

EMEA press release, April 2009

- Data from observational studies that have become available since April 2008, including the French Hospital Database on HIV, have continued to show a possible link between myocardial infarction and the use of abacavir. **Data from clinical trials showed low numbers of myocardial infarction and could not exclude a small increase in risk**
- However, the CHMP has concluded that there were inconsistencies between the different studies' findings, and that a causal relationship between treatment with abacavir and the risk of myocardial infarction can neither be confirmed nor refuted. To date, there is no established biological mechanism that could explain a potential increase in risk
- Nevertheless, when prescribing abacavir-containing medicines, prescribers should take action to minimise modifiable risk factors, such as smoking, high blood pressure and high blood-fat levels The product information for abacavir-containing medicines will be updated to reflect this information.

Tolérance et étude observationnelle

L’apport des études observationnelles en termes de tolérance

- Plus généralement admis, mais plutôt en raison de la puissance nécessaire
- No one questions the value of these epidemiologic studies when they’re used to identify the unexpected side effects of prescription drugs or to study the progression of diseases or their distribution between and within populations. Do We Really Know What Makes Us Healthy? By *G Taubes. New York times. September 16, 2007*
- Ne dédouane pas d’avoir la puissance suffisante

Combination Antiretroviral Therapy and the Risk of Myocardial Infarction

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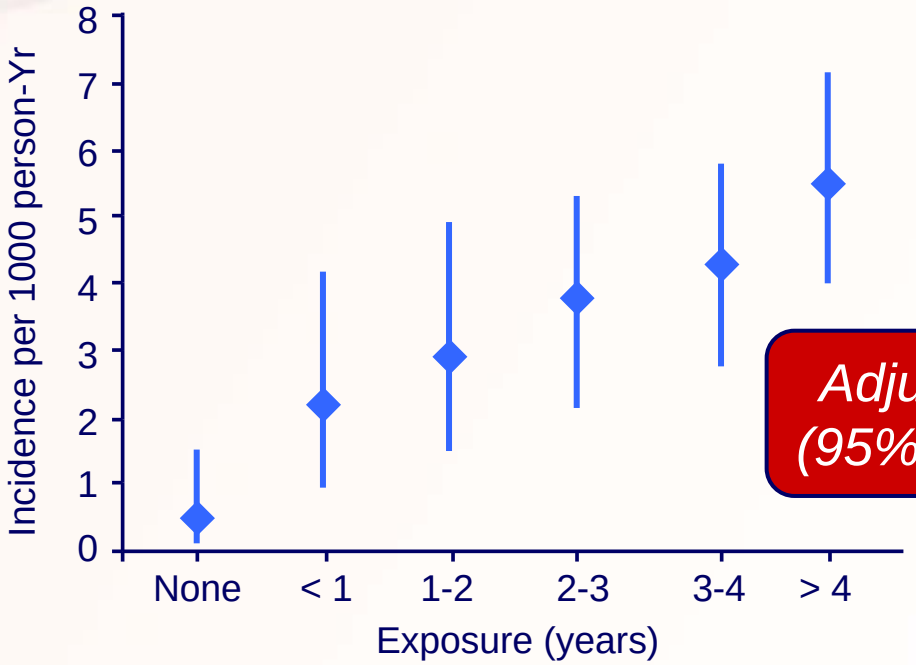

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Figure 1. Incidence of Myocardial Infarction According to the Duration of Exposure to Combination Antiretroviral Therapy.

126 cas et 36 199 patients années, durée d'exposition CART 1,9 ans

N Engl J Med 2003;349:1993-2003

The Veterans Administration database analysis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular and Cerebrovascular Events in Patients Treated for Human Immunodeficiency Virus Infection

Samuel A. Bozzette, M.D., Ph.D., Christopher F. Ake, Ph.D., Henry K. Tam, Ph.D., Sophia W. Chang, M.D., M.P.H., and Thomas A. Louis, Ph.D.

FEBRUARY 20, 2003

N Engl J Med 2003;348:702-10

The Veterans Administration database analysis

- Durée d'exposition 16 mois (26 957 P-A sous IP)
- HR: 1.23 (0.8-1.9)

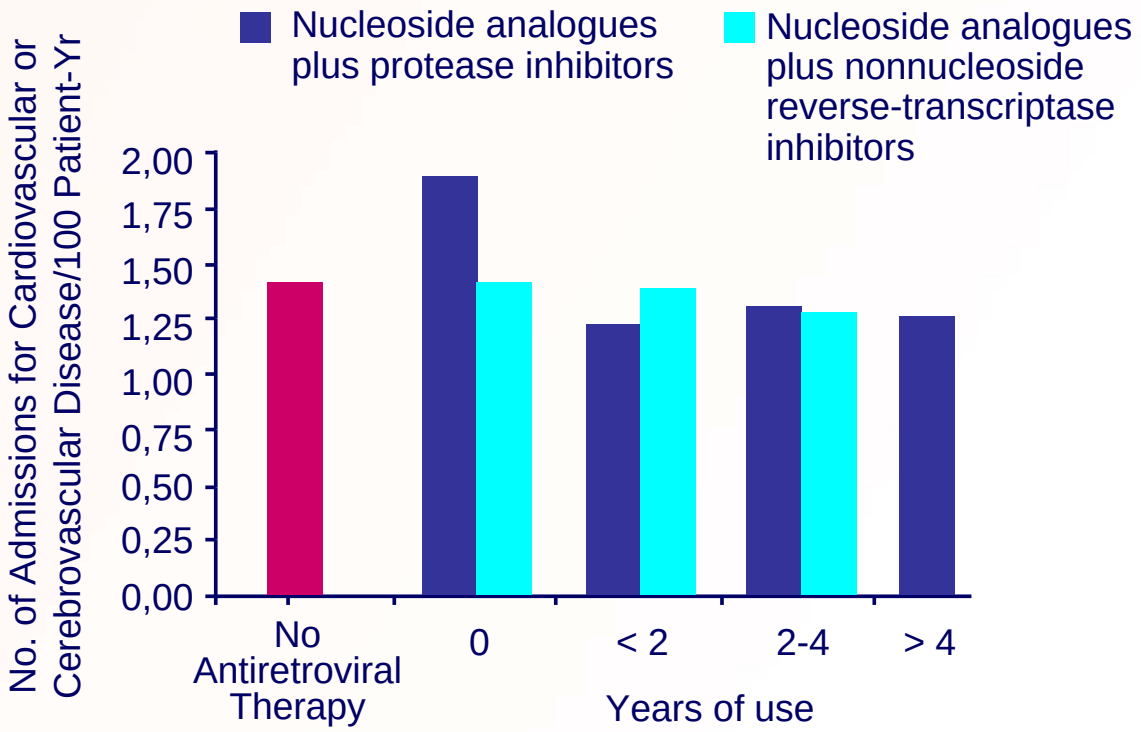

Figure 2. Rates of Admissions for Cardiovascular or Cerebrovascular Disease with Increasing Exposure to Combination Antiretroviral Therapy.

L’apport des études observationnelles en termes de tolérance

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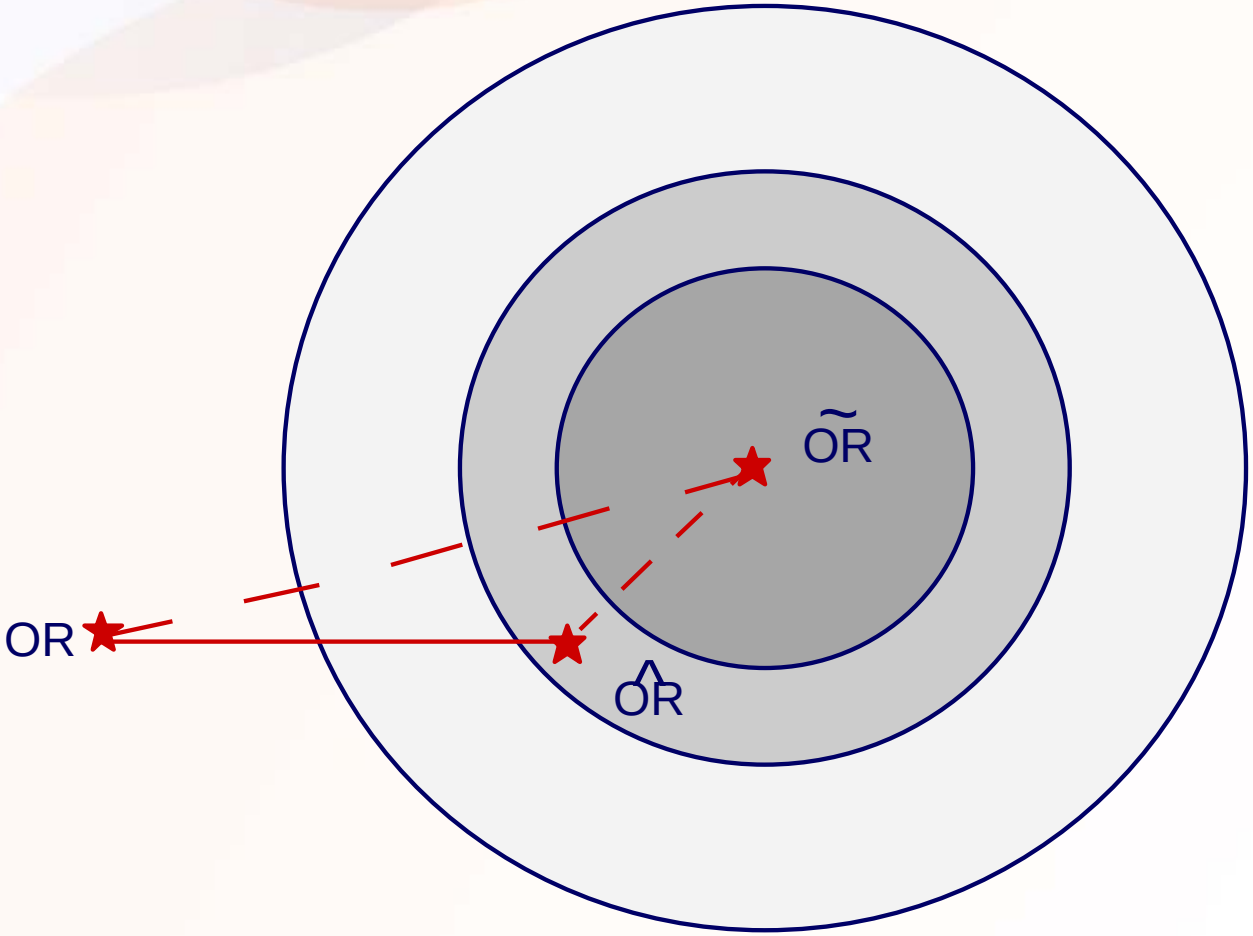
- Ne dédouane pas d’avoir la puissance suffisante

- Même s’Il peut y avoir des biais dans un essai avec tirage au sort, les biais sont classiquement plus important dans les études d’observations

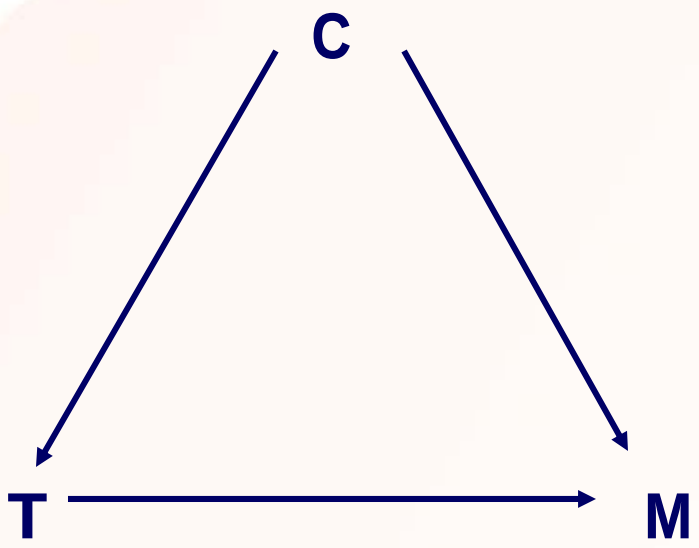
Biais



Biais en épidémiologie

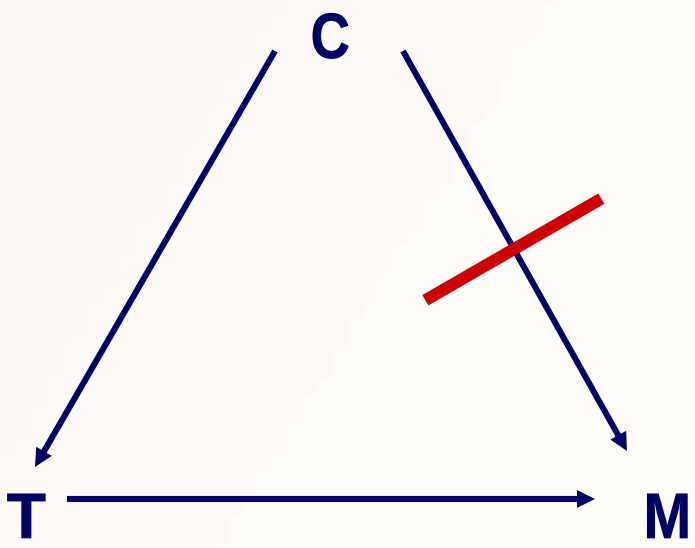
- biais de sélection
- biais de classification
- facteurs de confusion

Facteur de confusion



- Définition
  - facteur de risque
  - lié à l'exposition
  - non intermédiaire
- Prise en compte
  - schéma, appariement, analyse
- Relation traitement ARV et IdM
  - tabac ?
  - âge ?
  - cholestérol ?

Analyse multivariée (ajustée)



Facteurs de confusion et traitement

- Confusion par indication
  - Effet indésirable associé à la maladie que le traitement est censé soigner

- « Channeling bias »
  - Biais de sélection qui survient quand 2 traitements ayant la même indication sont prescrits à des patients dont le pronostic n'est pas le même

Strobe - 1

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies

Erik von Elm, Douglas G Altman, Matthias Egger, Stuart J Pocock, Peter C Gøtzsche, Jan P Vandenbroucke, for the STROBE initiative

Un exemple en dehors du VIH

Maladie thromboembolique veineuse et contraceptifs oraux

In the mid-1990, all but one studies reported a higher risk of venous tromboembolism for 3rd generation oral contraceptives compared with 2nd generation

- Rate ratios 1.5 to 3 after adjustment
- Various settings, both case-control and cohort design
- Inconsistent for the impact of duration of use
- Reanalysis restricted on first time users of one of the study

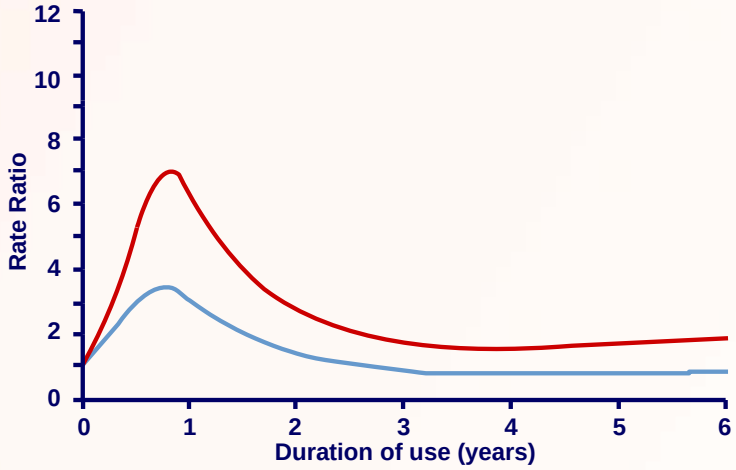


Figure 1. Crude rate ratio of venous thromboembolism as a function of duration of second generation (blue line) and third generation (red line) oral contraceptive use among first-time users compared with nonusers. Rate ratio fitted by quadratic splines using logistic regression.

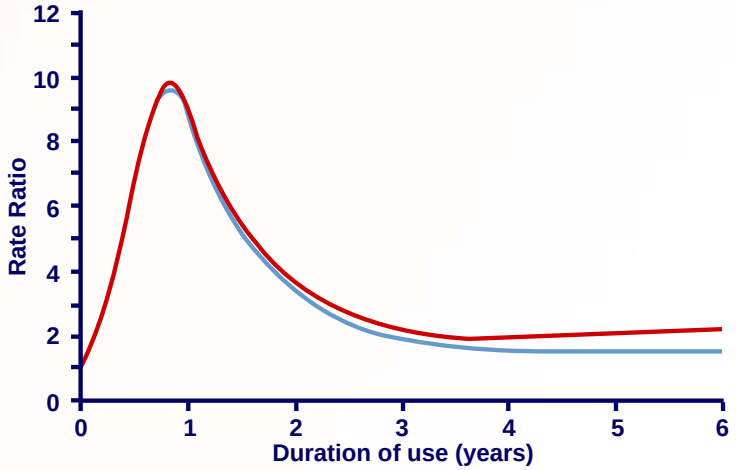


Figure 2. Adjusted rate ratio of venous thromboembolism as a function of duration of second generation (blue line) and third generation (red line) oral contraceptive use among first-time users compared with nonusers. Rate ratio, adjusted for linear age, smoking, alcohol use, study center, and body mass index, fitted by quadratic splines using logistic regression.

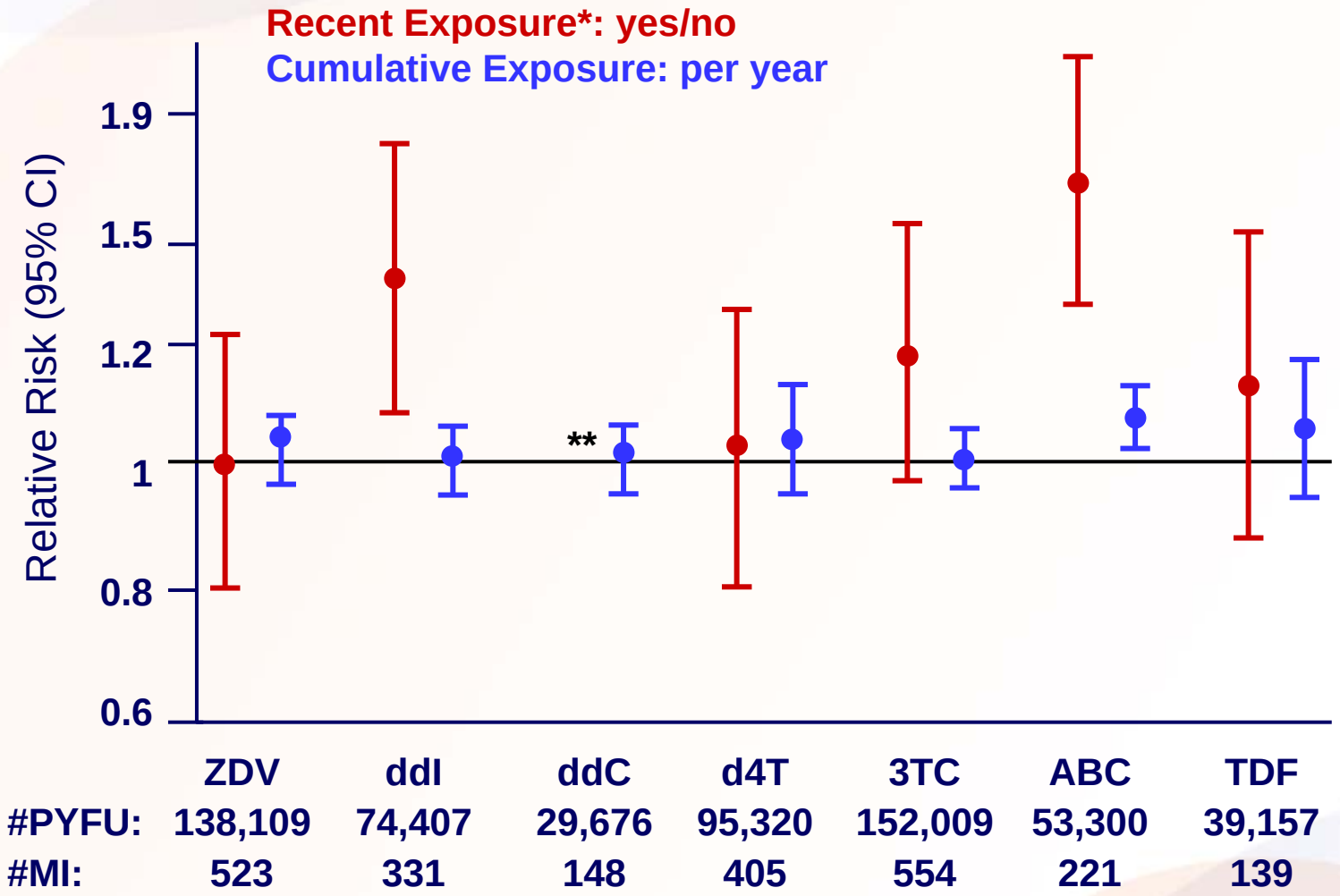
Suissa S et al, Contraception 1997; 56:141-146

D:A:D Study: Methods

- 33 308 patients from 11 cohorts included
- Follow-up counted from D:A:D enrollment until the first MI event, 1st February 2008, or 6 months after the patient's last clinic visit (whichever occurred first)
- All models include adjustment for:
  - Demographics
  - Cardiovascular risk factors
  - Use of other ARTs
- Further analyses included adjustment for:
  - Latest measure of lipids
  - Metabolic parameters
  - CD4
  - HIV-RNA

Lundgren JD, et al. 16th CROI; Montreal, Canada; February 8-11, 2009. Abst. 42LB.

D:A:D Study: NRTIs and Risk of MI



* Recent use=current or within the last 6 months. **Not shown (low number of patients currently on ddC)

FHDH ANRS CO4: MI Case Control Study

- Nested, case-control study to evaluate association between risk of MI and
  - Cumulative exposure to specific NRTIs
  - Recent (current or within last 6 months) and past exposure (>6 months ago) to specific NRTIs
  - Cumulative to specific NNRTIs
  - Cumulative exposure to specific Pis
- 74 958 HIV-infected patients followed between 2000 and 2006
  - Cases: 289 Patients with a first definite or probable MI prospectively reported between January, 2000 and December, 2006
  - Matched Controls: For each MI case, up to 5 controls with no history of MI matched for age, sex and clinical center, followed at time of the corresponding case MI
- Data collected for cases and controls
  - Cardiovascular risk factors and treatments
  - HIV history and treatment checked

Lang S, et al .16th CROI; Montreal, Canada; February 8-11, 2009. Abst . 43LB.

Comparaison

- FHDH
- 73% of patients naive at enrollment in the cohort
- First MI between 2000 and 2006
  - Prior MI excluded
- Adjustment on IV drug and/or cocaine use
- Adjustment on HIV factors in main analyses
- Only Nice participates in both studies
  - 1 common case

- D:A:D
- 73% of patients already exposed at enrollment in the cohort
- MI after enrollment
  - Prior MI non excluded
- Adjustment on transmission group
- Not adjustment on HIV factors in main analyses
- ddI?

Que conclure sur l'exemple ?

- Plus d'effets des facteurs de confusion pour les NRTIs, en particulier abacavir et tenofovir que pour les NNRTIs ou les IPs
- Les résultats des études seront plus concordantes pour les NNRTIs et les IPs que pour les NRTIs
- Les résultats pour les NRTIs peuvent dépendre de différences sur le schéma des études et la prise en compte des facteurs de confusion
  - Cela peut expliquer l'association avec ddI observée dans DAD mais ni dans SMART ni dans FHDH
  - Cela peut expliquer la différence des résultats entre les études sur abacavir

Abacavir and the risk of heart attack

EMEA press release, April 2009

- Data from observational studies that have become available since April 2008, including the French Hospital Database on HIV, have continued to show a possible link between myocardial infarction and the use of abacavir. Data from clinical trials showed low numbers of myocardial infarction and could not exclude a small increase in risk
- However, the CHMP has concluded that there were **inconsistencies** between the different studies' findings, and that **a causal relationship** between treatment with abacavir and the risk of myocardial infarction **can neither be confirmed nor refuted**. To date, there is **no established biological mechanism** that could explain a potential increase in risk
- Nevertheless, when prescribing abacavir-containing medicines, prescribers should take action to minimise modifiable risk factors, such as smoking, high blood pressure and high blood-fat levels The product information for abacavir-containing medicines will be updated to reflect this information.

Conclusion

- Dans l'étude de la tolérance, essais et études observationnelles sont complémentaires et répondent à des questions différentes
- Le problème essentiel des études d'observation est la gestion des biais par le schéma et l'analyse, sans oublier de vérifier la puissance de l'étude ou sa pertinence
- Le respect des recommandations existantes sur la présentation des résultats est important pour juger de la qualité des études

Backup

Strobe - 2

Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) *Cohort study*—give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—give the eligibility criteria, and the sources and methods of selection of participants
		(b) *Cohort study*—for matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—for matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
		(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(d) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(e) Describe any sensitivity analyses

Strobe - 3

Results		
Participants	13*	(a) Report the numbers of individuals at each stage of the study—eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate the number of participants with missing data for each variable of interest
		(c) Cohort study—summarise follow-up time (eg, average and total amount)
Outcome data	15*	Cohort study—report numbers of outcome events or summary measures over time Case-control study—report numbers in each exposure category, or summary measures of exposure Cross-sectional study—report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(b) Report category boundaries when continuous variables were categorised
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results