

A decorative graphic consisting of a thin blue arc at the top left that curves downwards and to the right, transitioning into a larger, semi-transparent blue shape that tapers towards the right edge of the slide.

# Introduction to Clinical Research

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# Study types

- **Observational studies**

- **Cross-sectional study** (description of a population, validation of a test, a diagnostic strategy)
- Case-control study (association)
- **Cohort study** (association)
  - Retrospective/prospective

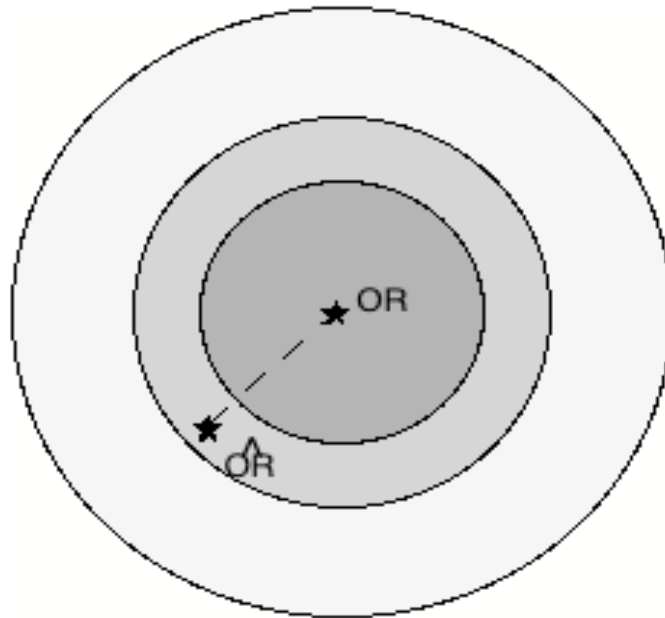
- **Clinical trials** (evaluation of a treatment, a strategy, a practice)

- Phase 1, 2, 3, 4

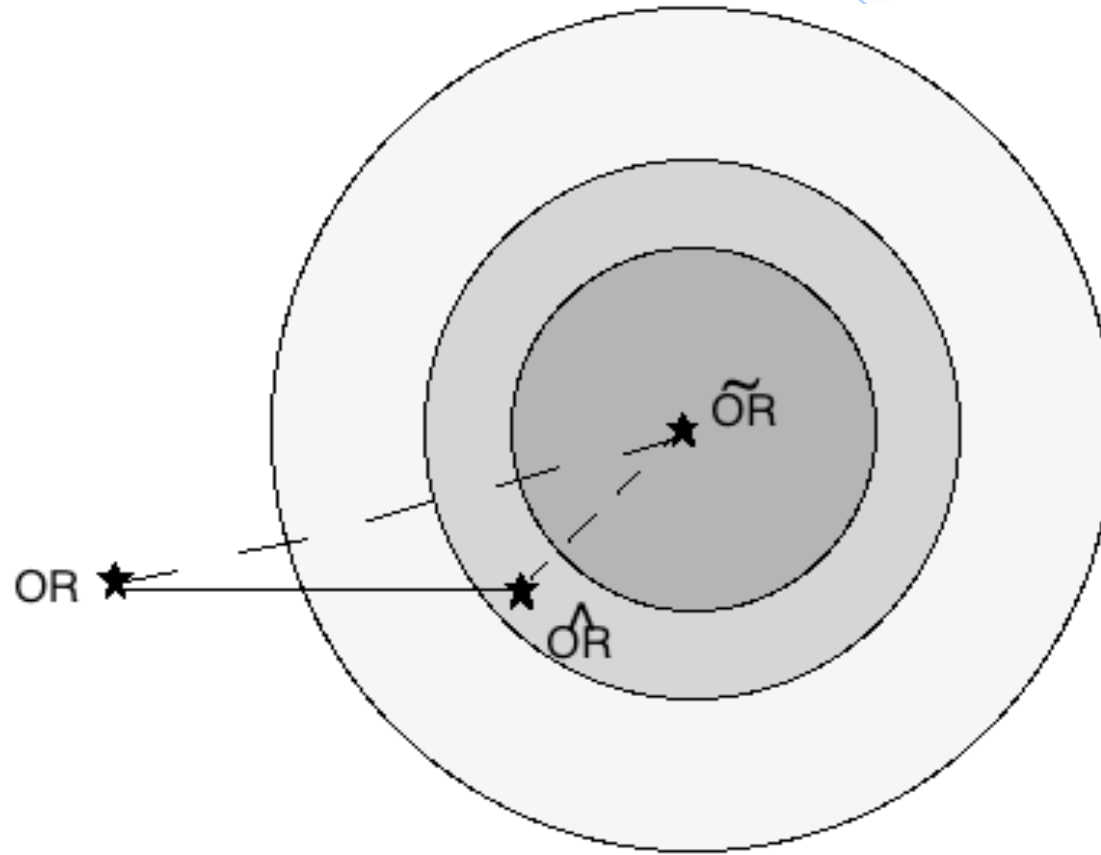
# Target population, source population

- Target population : population to whom one would like to apply the results
- Source population : population where the study sample was selected

# Sampling variability



# Bias

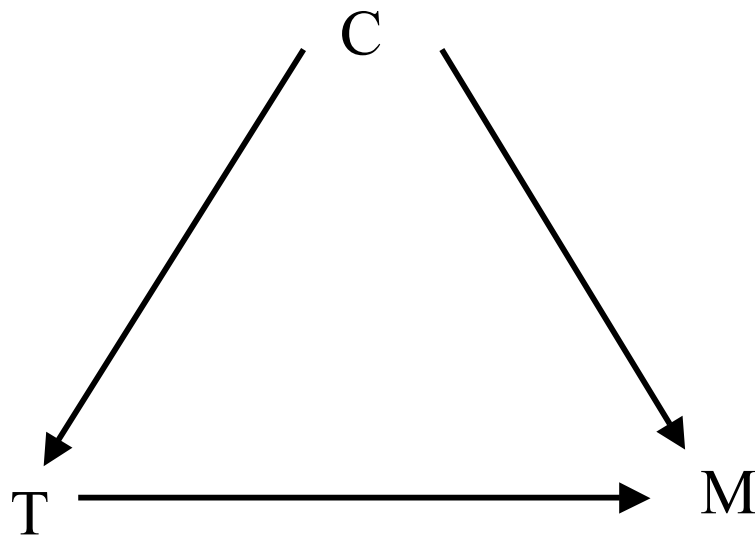




# Bias

- Selection bias
- Classification bias
- Confounding factor
  - Risk factor
  - Associated with exposition
  - Not on the causal pathway

# Confounding Indication bias



# Validation of a diagnostic procedure - 1

- Validation of a test or a diagnostic strategy versus a gold standard
  - Sensitivity : Probability of concluding 'disease' when present
  - Specificity : Probability of concluding 'free of disease' when the disease is not present
  - Predictive values
    - Positive: Probability of having the disease when the test is positive
    - Negative: Probability of not having the disease when the test is negative
  - Likelihood ratio
    - of a positive test:  $Se/(1-Sp)$
    - Of a negative test:  $Sp/(1-Se)$
  - ROC curve
    - Graph displaying Se as a function of  $1-Sp$

# Validation of a diagnostic procedure - 2

- Protocol

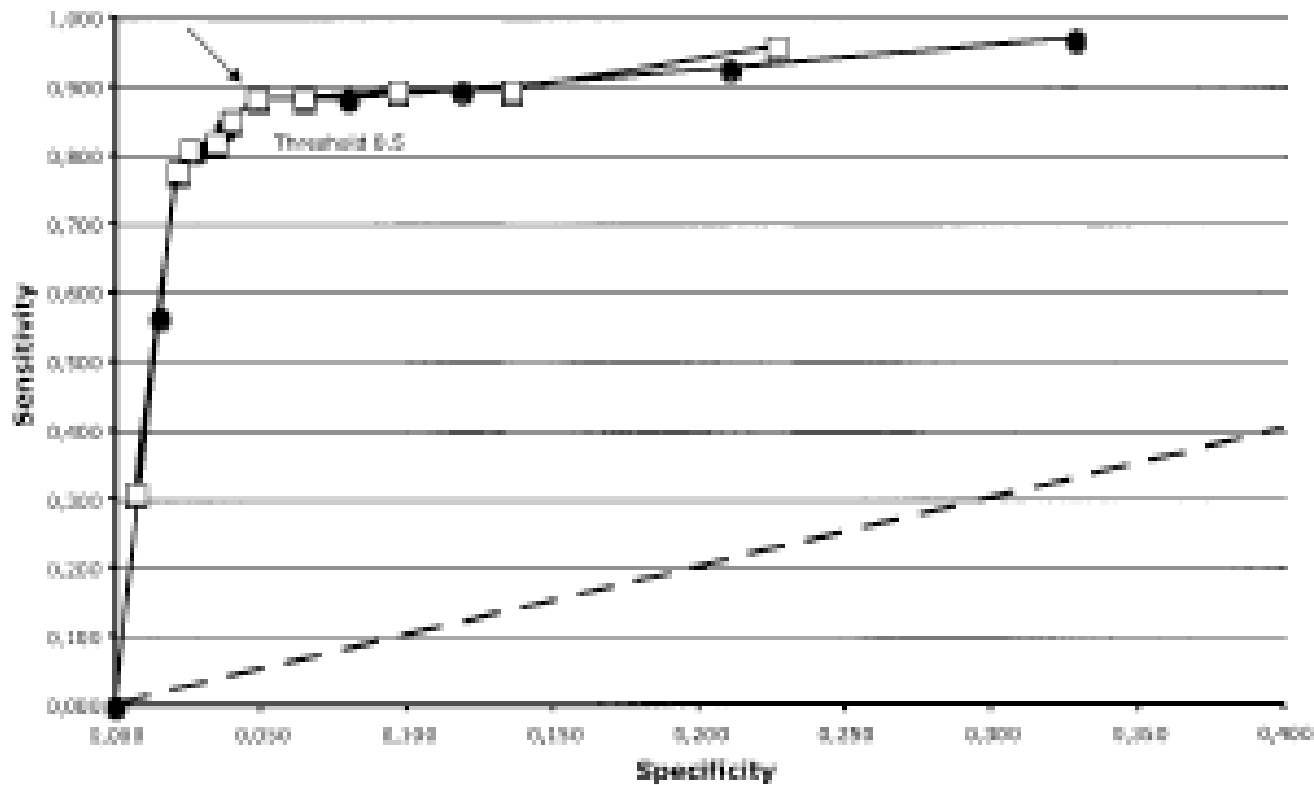
- Inclusion and non inclusion criteria
- New procedure and gold standard in all included subjects
- Blinding
- Independent validation sample
- Se, Sp (with 95% CI), ROC curves and/or Likelihood ratios

## Development and Validation of an Immunoassay for Identification of Recent Human Immunodeficiency Virus Type 1 Infections and Its Use on Dried Serum Spots

Francis Barin,<sup>1\*</sup> Laurence Meyer,<sup>2</sup> Rémi Lancar,<sup>3</sup> Christiane Deveau,<sup>2</sup> Myriam Gharib,<sup>2</sup> Anne Laporte,<sup>4</sup> Jean-Claude Desenclos,<sup>4</sup> and Dominique Costagliola<sup>3</sup>

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# Example : Identification of recent HIV infection (<6 months)

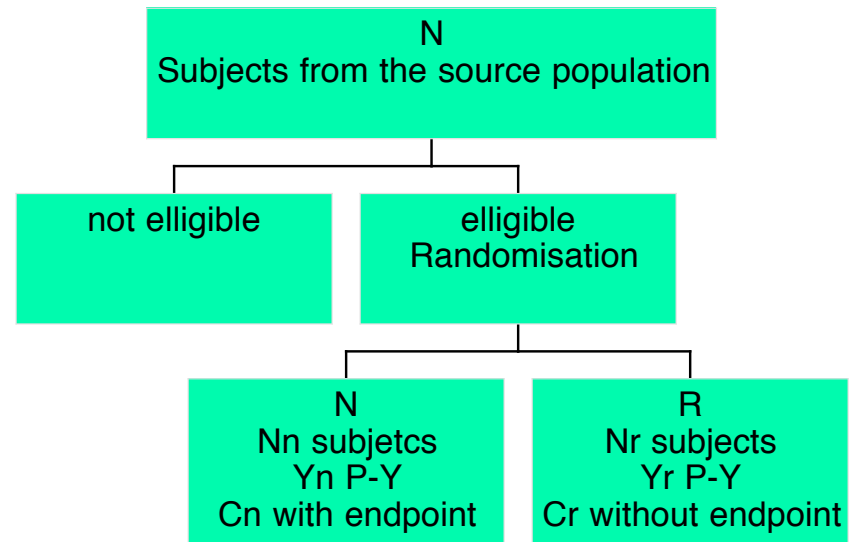


# Example : Identification of recent HIV infection (<6 months)

TABLE 2 Area under the ROC curve and sensitivity and specificity for each antigen or combination of antigens on the validation sample when using a threshold of 0.5

Antigen or combination	Validation sample		Validation sample parameter (with threshold of 0.50)			
	Area under the ROC curve	SE	Sensitivity at $\leq 180$ days	Specificity at $> 180$ days	Specificity	
					Chronic patients	AIDS patients
IDE	0.946	0.015	88.3	100	95.6	86.7
V3	0.936	0.016	83.0	95.8	96.0	80.4
IN	0.831	0.021	62.8	87.5	88.2	75.5
p24	0.380	0.021	0	100	68.0	97.2
IDE + V3	0.949	0.014	88.3	100	97.6	86.0
IDE + IN	0.945	0.014	85.1	100	95.4	81.1
IDE + p24	0.944	0.015	88.3	100	95.4	94.4
V3 + IN	0.938	0.016	86.2	100	96.2	80.4
V3 + p24	0.937	0.017	81.9	100	96.8	93.0
IN + p24	0.778	0.022	26.6	100	88.0	95.1
IDE + V3 + IN	0.949	0.014	86.2	100	97.2	84.6
IDE + V3 + p24	0.952	0.015	84.0	100	97.6	96.5
IDE + IN + p24	0.938	0.015	80.9	100	96.2	94.4
V3 + IN + p24	0.931	0.017	78.7	100	96.0	95.1
All four	0.943	0.015	79.8	100	97.0	95.1

# Clinical trial - 1



# Clinical trial - 2

## Bias

- Minimisation of bias
  - Randomisation
    - Selection bias at baseline, confounding
  - Blinding
    - Classification bias
- Selection bias
  - Lost to follow-up

# Clinical trial - 3

## Objectives

- Trials comparing a new treatment (or a strategy) to a reference treatment
  - Showing the superiority of the new treatment
    - Is N better than R ?
      - Pre-treated patients
  - Showing the non-inferiority of the new treatment
    - Is N doing not worse than R ?
      - Naive patients
  - Showing the equivalence of the new treatment
    - Is N doing as well as (neither better not worse) R ?
      - Bio-equivalence (different formulation of the same dru)

# Example - 1

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Tenofovir DF, Emtricitabine, and Efavirenz vs. Zidovudine, Lamivudine, and Efavirenz for HIV

Joel E. Gallant, M.D., M.P.H., Edwin DeJesus, M.D., José R. Arribas, M.D., Anton L. Pozniak, M.D., Brian Gazzard, M.D., Rafael E. Campo, M.D., Biao Lu, Ph.D., Damian McColl, Ph.D., Steven Chuck, M.D., Jeffrey Enejosa, M.D., John J. Toole, M.D., Ph.D., and Andrew K. Cheng, M.D., Ph.D.,  
for the Study 934 Group\*

# Example - 2

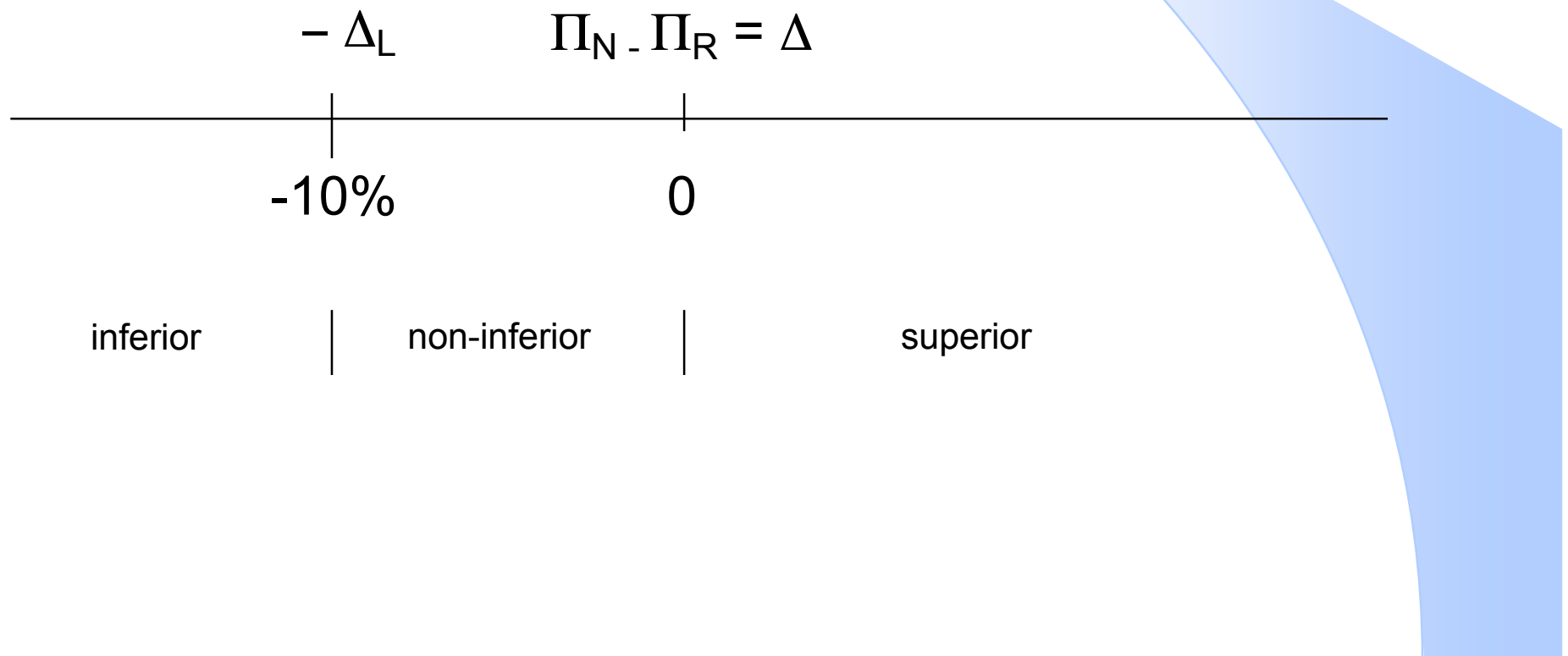
## **EFFICACY ANALYSIS**

The primary objective was to assess the noninferiority of the regimen of tenofovir DF, emtricitabine, and efavirenz to the regimen of zidovudine, lamivudine, and efavirenz as measured by HIV RNA levels of less than 400 copies per milliliter through week 48, defined according to the algorithm of the Food and Drug Administration (FDA) for the time to loss of virologic response, which requires confirmation (two consecutive values) of response or of no response (missing data or early termination of participation in the study was considered to be failure).<sup>5</sup> The 487 eligible patients without baseline resistance to efavirenz who underwent randomization and received treatment were the predefined population for the primary end-point analysis. The secondary objective was to assess the noninferiority of tenofovir DF, emtricitabine, and efavirenz to zidovudine,

lamivudine, and efavirenz as assessed by HIV RNA levels of less than 50 copies per milliliter and changes in the CD4 cell count.

# Definition of non-inferiority

- N is not doing worse than R



# Comparison test

- Superiority (two-sided)
  - $H_0 : \Pi_N = \Pi_R$
  - $H_1 : \Pi_N \neq \Pi_R$
- Superiority (one-sided)
  - $H_0 : \Pi_N = \Pi_R$
  - $H_1 : \Pi_N > \Pi_R$
- Non inferiority (one-sided)
  - $H'_0 : (\Pi_N - \Pi_R) = \Delta < -\Delta_L$  (N is inferior to R)
  - $H'_1 : (\Pi_N - \Pi_R) = \Delta \geq -\Delta_L$  (N is non inferior or superior R)
  - The non inferiority limit  $\Delta_L$  influences the result of the analysis

# Choice of the non-inferiority limit - 1

- Clinical decision, not statistical
- The largest difference clinically acceptable
- $\leq$  difference used in superiority trials of the same domain
- To warrant that the new product is doing better than a placebo in trials with no placebo

# A working case in diabetes: HbA1c the risk of death - 1

- In diabetes, for new drugs the most common endpoint is HbA1C
  - Non inferiority margin usually taken as 0.6 %
  - Superiority trials usually try to demonstrate a 1% difference

# A working case in diabetes: HbA1c the risk of death - 2

- Each 1% reduction in updated mean HbA1c was associated with reductions in risk of
  - 21% for any end point related to diabetes (95% confidence interval 17% to 24%),
  - 21% for deaths related to diabetes (15% to 27%),
  - 14% for myocardial infarction (8% to 21%), and
  - 37% for microvascular complications (33% to 41%).
  - No threshold of risk was observed for any end point.

# A working case in diabetes: HbA1c the risk of death - 3

- Is it possible to define a non-inferiority limit clinically acceptable in this context?

## Choice of the non-inferiority limit - 2

- As defining a non-inferiority limit implies to accept some loss
  - There must be some advantage to use the new product
    - easiness
    - safety
    - costs
    - ...

# Clinical trial - 3

## Protocol

- Justification, hypothesis
- Objective of the trial
  - More than one question
  - Parallel or cross-over
  - Superiority, non-inferiority, equivalence
- Primary endpoint
- Inclusion and non-inclusion criteria
- Follow-up, AE and SAE
- Sample size, analysis plan

# Clinical trial - 5

## Sample size

- Difference in superiority trial, non-inferiority limit in non-inferiority trial
- Type I error, Power
- Expected success rate in the reference group
- For a non inferiority trial

# Example

Table 2. Sample sizes per arm for noninferiority trials, by power, delta and expected response rate in the control arm; the efficacy of the new drug is assumed to be equivalent for the purposes of calculating sample sizes.

Expected response rate in control arm	Delta 12%	80% power	90% power	Delta 10%	80% power	90% power
50%	273		365	393		526
55%	270		362	389		521
60%	262		351	377		505
65%	249		333	358		479
70%	229		307	330		442
75%	205		274	295		395
80%	175		234	252		337
85%	139		187	201		268
90%	99		132	142		190

# Clinical trial - 6

## Study follow-up

- Monitoring
- Change
  - in inclusion and non inclusion criteria
  - in sample size
  - in endpoint
- Interim analysis
- DSMB

# Clinical trial - 7

## Analysis

- Analysis plan in the protocol
- ITT and per protocol analysis
- Sub-group analysis
- Adjusted analysis

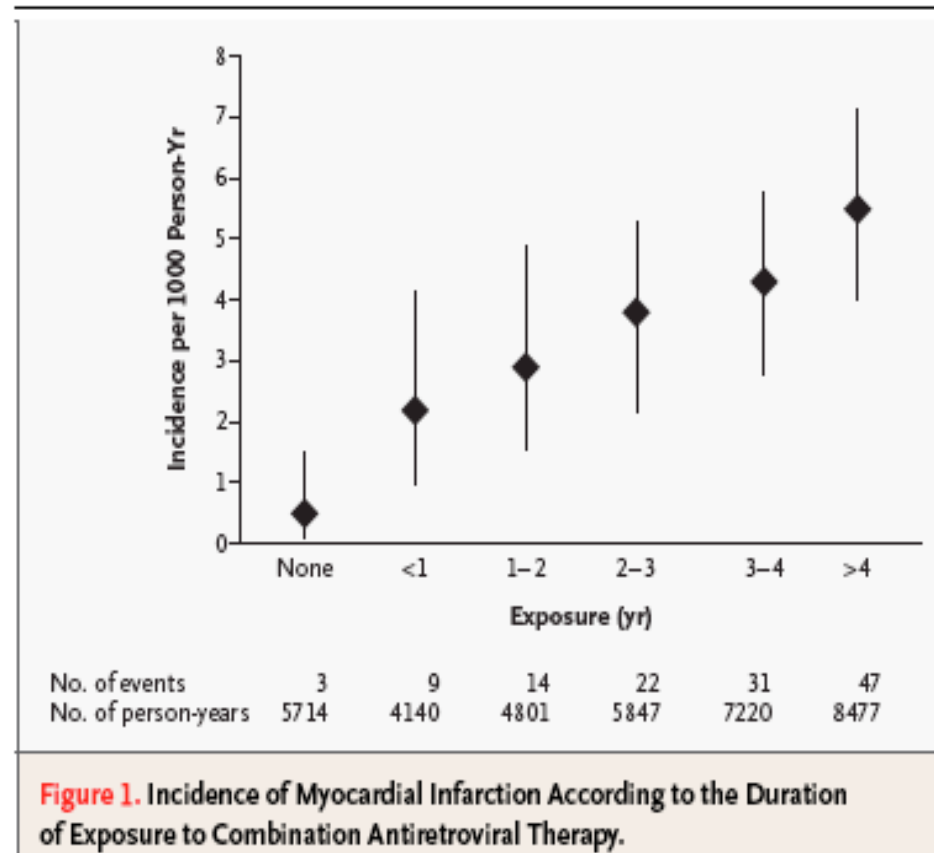
# Clinical trial - 8

## Advantages and limits

- Useful if
  - Randomisation is possible (equipoise)
- Advantage +++
  - **Causal interpretation**
- Limits
  - Costs and duration
  - Logistic
  - Bias possible during the study
  - **No power for rare adverse events**

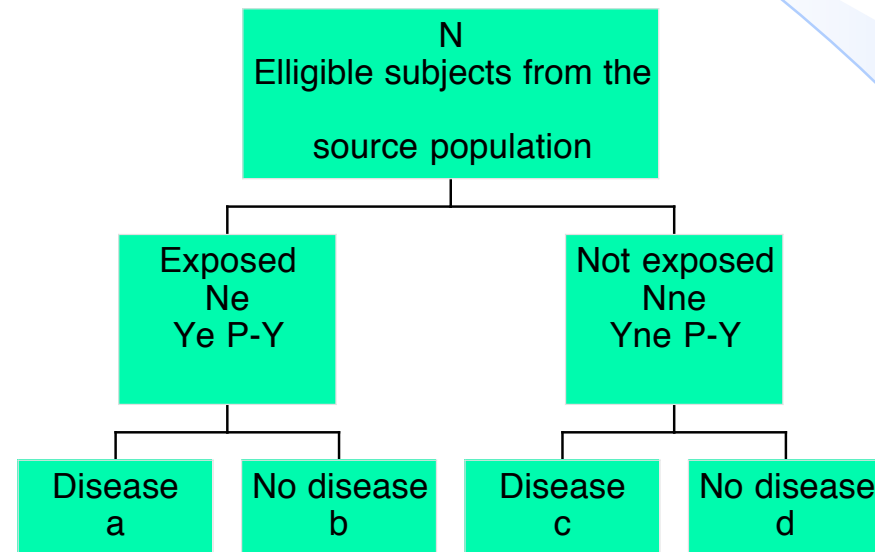
# Combination Antiretroviral Therapy and the Risk of Myocardial Infarction

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



126 cases and 36 199 patients-years versus around 600 subjects for 2 years

# Cohort - 1



$$I_e = a/Y_e \text{ et } I_{ne} = b/Y_{ne}$$

$$RR = \text{relative risk} = I_e/I_{ne}$$

# Cohort - 2 Protocol

- Enrolment
  - population
  - register
  - Database
- A priori evaluation of exposure
- Follow-up
  - Disease status (register ?)

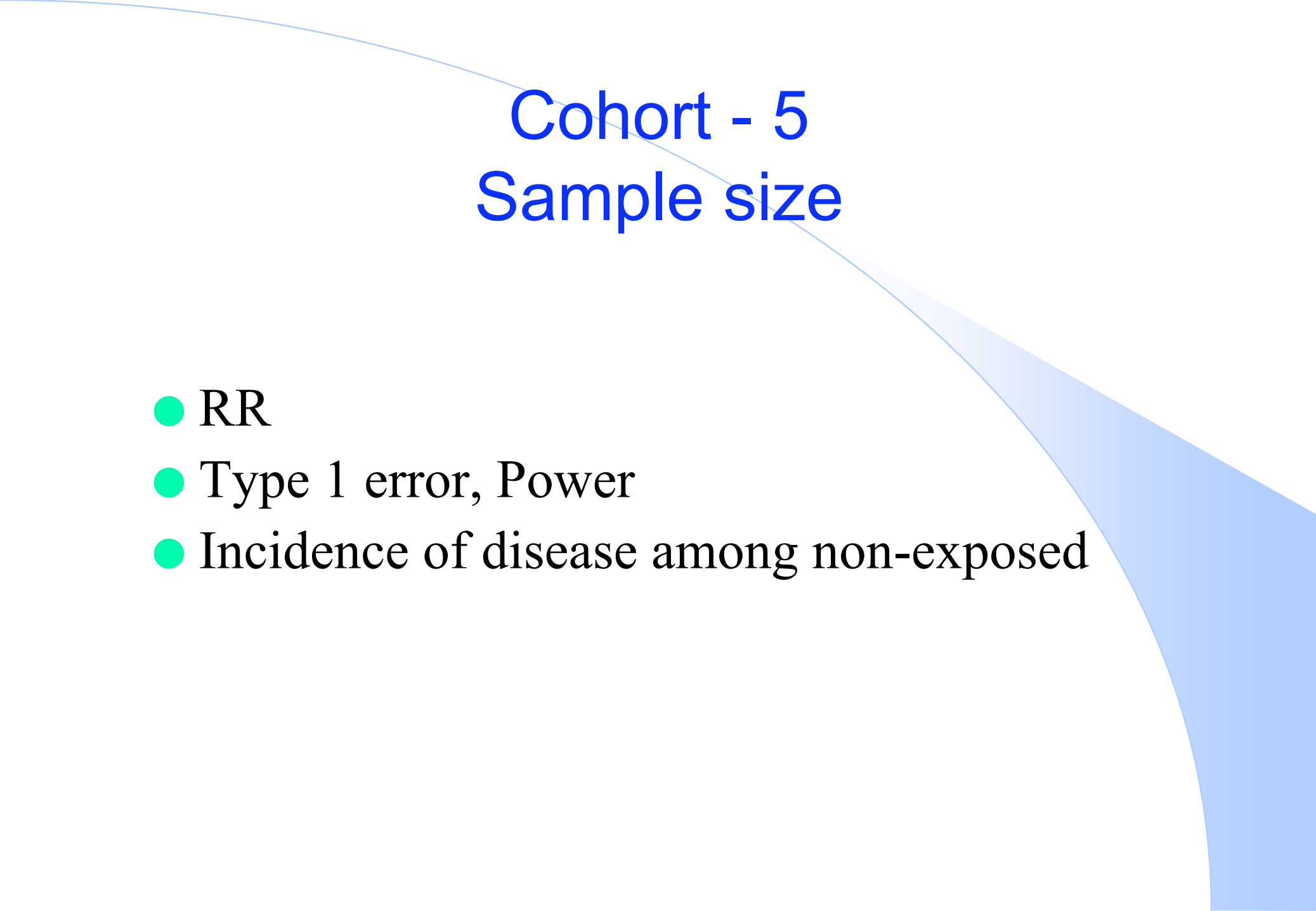
# Cohort - 3 Bias

- Selection bias
  - healthy worker effect
  - lost-to-follow-up
- Classification bias
  - On the disease status differential or not

# Cohort - 4

## Confounding

- Selection on a factor
- (Matching)
- Adjustment



# Cohort - 5 Sample size

- RR
- Type 1 error, Power
- Incidence of disease among non-exposed

# D:A:D: Hypothesis and methods

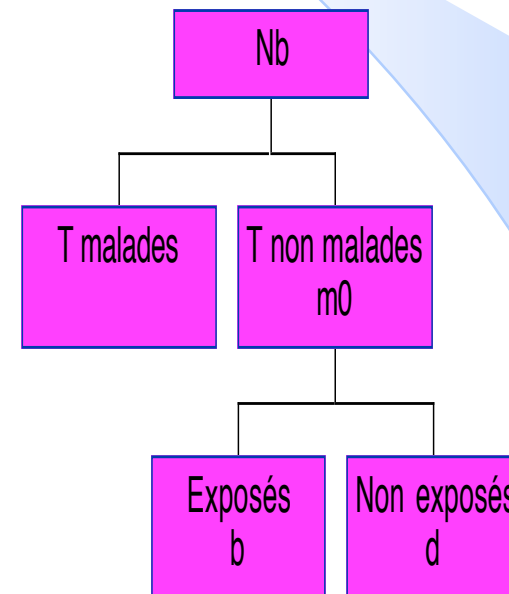
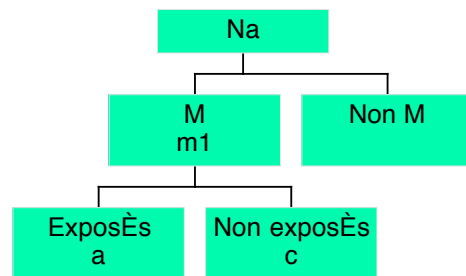
- Primary hypothesis: CART increases the risk of myocardial infarction (MI) (at least 2-fold) over and above the contribution from age and other demographic risk factors. Required 100 primary events for sufficient power:
  - # of events and comparison of incidence of MI and ART history remained blinded until hypothesis could be tested
  - Follow-up until Feb 2002 allowed for sufficient # of events to test hypothesis – results reported in NEJM, Nov 2003
  - Study continues
- Prospective, multinational study - 11 cohorts from Europe, Australia and USA
- Information collected: HIV-related and ART, risk and occurrence of CVD and diabetes mellitus
- Extensive training and quality control programme

# Cohort - 6

## Advantages and limits

- Useful if
  - Several diseases, several questions
  - Delay between exposure and disease not too long
  - Rare exposition
- Advantage (versus case-control)
  - Incidence can be estimated
  - a priori evaluation of exposure
- Limits
  - Duration and costs
  - Lost to follow-up
  - Bias on disease status

# Etude cas témoins - 1



$$e1 = a/m1 \text{ et } e0 = b/m0$$

$$\text{OR} = \text{odds ratio} = [e1/(1-e1)]/[e0/(1-e0)] = ad/bc$$

# Objectifs du projet

- Déterminer, après 10 ans d'utilisation des combinaisons d'antirétroviraux (cART),
  - les facteurs de risque de survenue de l'infarctus du myocarde (IdM) dans une population infectée par le VIH
  - Facteurs de risque liés à l'infection
    - en raison de l'inflammation chronique liée au VIH
    - CD4, charge virale
  - Facteurs de risque liés aux ARV,
    - en particulier rôle spécifique des nRTI
    - Impact des nouveaux ARV présentant moins d'effets secondaires lipidiques

# Cas témoins - 2

## Protocole

- Choix des malades
  - population
  - registre
  - hôpital
- Choix des témoins
  - plus d'un témoin par cas ?
- Mesure de l'exposition à posteriori

# Schéma de l'étude

- Etude cas-témoins nichée dans la cohorte FHDH, entre 2000 et juin 2006
- 3 témoins par cas appariés sur sexe, âge  $\pm 3$  ans et centre, et déjà suivi au moment de l'infarctus du cas correspondant
  - Etude pour déterminer critères d'appariement des témoins (*Pharmacoepidemiology and drug safety, 2008*)
- Retour au dossier
  - Validation des cas
  - Antécédents et facteurs de risque CV
  - Prise en charge des maladies cardiovasculaires (traitements spécifiques)
  - Biologie (cholestérol, triglycérides, glycémie)

# Cas témoins - 3

## Biais

- Biais de sélection
  - biais d'indication
  - non réponse
- Biais de classification
  - erreur sur l'exposition différentielle (sous ou surestimation) ou non (sous estimation)

# Cas témoins - 4

## Facteurs de confusion

- Sélection sur un facteur
- appariement
  - par strate
  - individuel
  - surappariement
- ajustement

# Cas témoins - 5

## Nombre de sujets

- OR
- Risque première espèce, Puissance
- fréquence d'exposition chez les témoins
- OR=2, Bilatéral, P=80%  $Pe_T=0.20$ , 1 témoin par cas 170 cas et 170 témoins
- Egalité des groupes
- nombre de témoins par cas

# Quel OR pourra être mis en évidence ?

- Avec 290 cas et 870 témoins
- Puissance de 80%
- Soit  $p$  la proportion d'exposés dans le groupe témoin

p	0.01	0.05	0.10	0.15	0.20	0.25	0.30	0.40	0.50
OR	4.13	2.14	1.79	1.66	1.58	1.53	1.50	1.48	1.48

# Cas témoins - 6

## Avantages et limites

- Adapté si
  - maladie rare
  - délai exposition maladie long
  - une maladie plusieurs facteurs
- Avantages
  - Pas de suivi
  - Nombre de sujets plus faibles pour un nombre de cas donné
- Limites
  - biais d'indication
  - détermination a posteriori de l'exposition

# Interpretation of the results

- Statistical significance
  - Value or the measure of association not just significant on not
- Causal interpretation
  - Easy in a well conducted trial
    - However 2 two trials on the same topic may have discordant results
      - ACTG 5202 and Heat
  - In observational studies
    - Coherence
    - Minimisation of selection and classification bias and confounding
    - Plausibility
- Extrapolation