

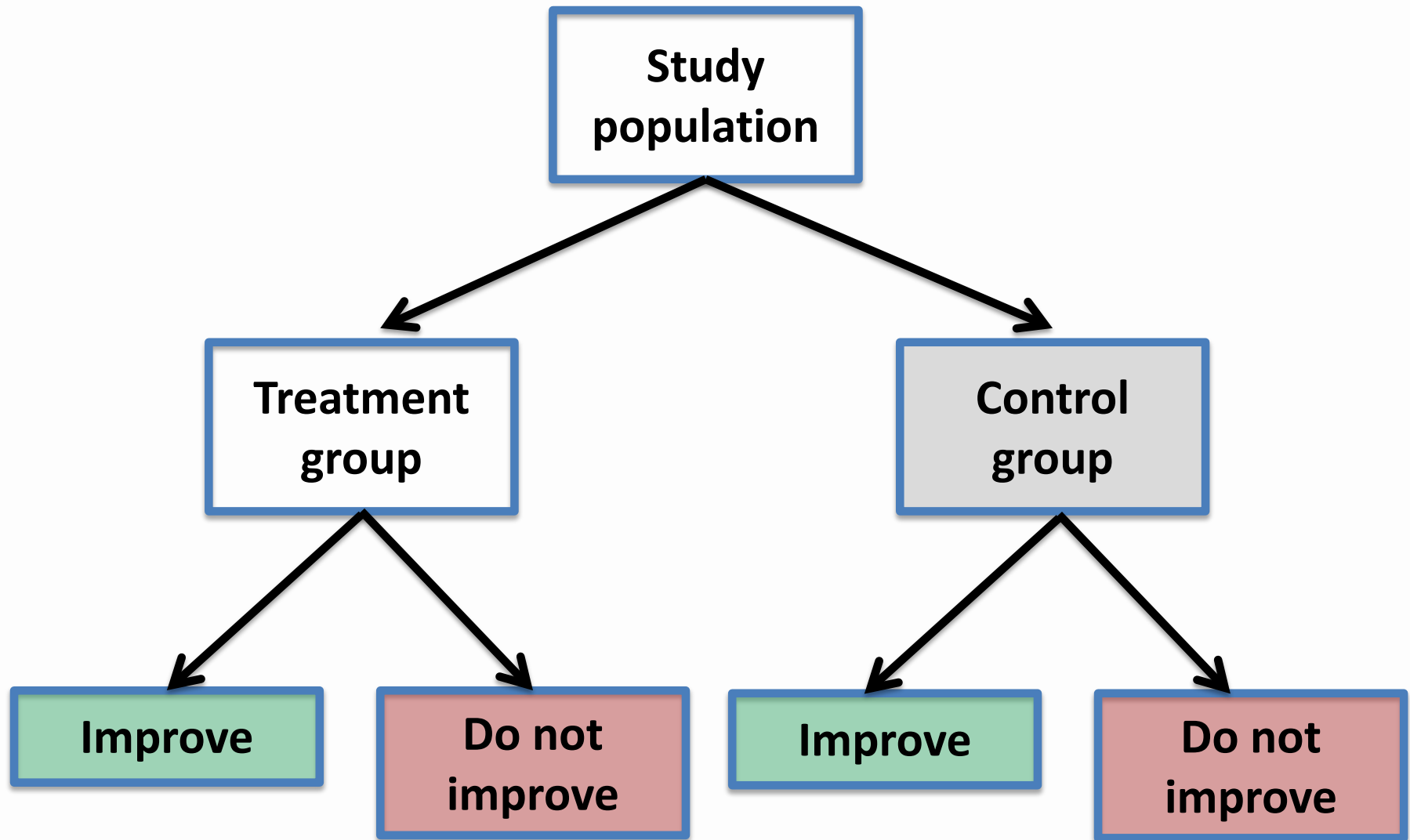
Randomized controlled trials II

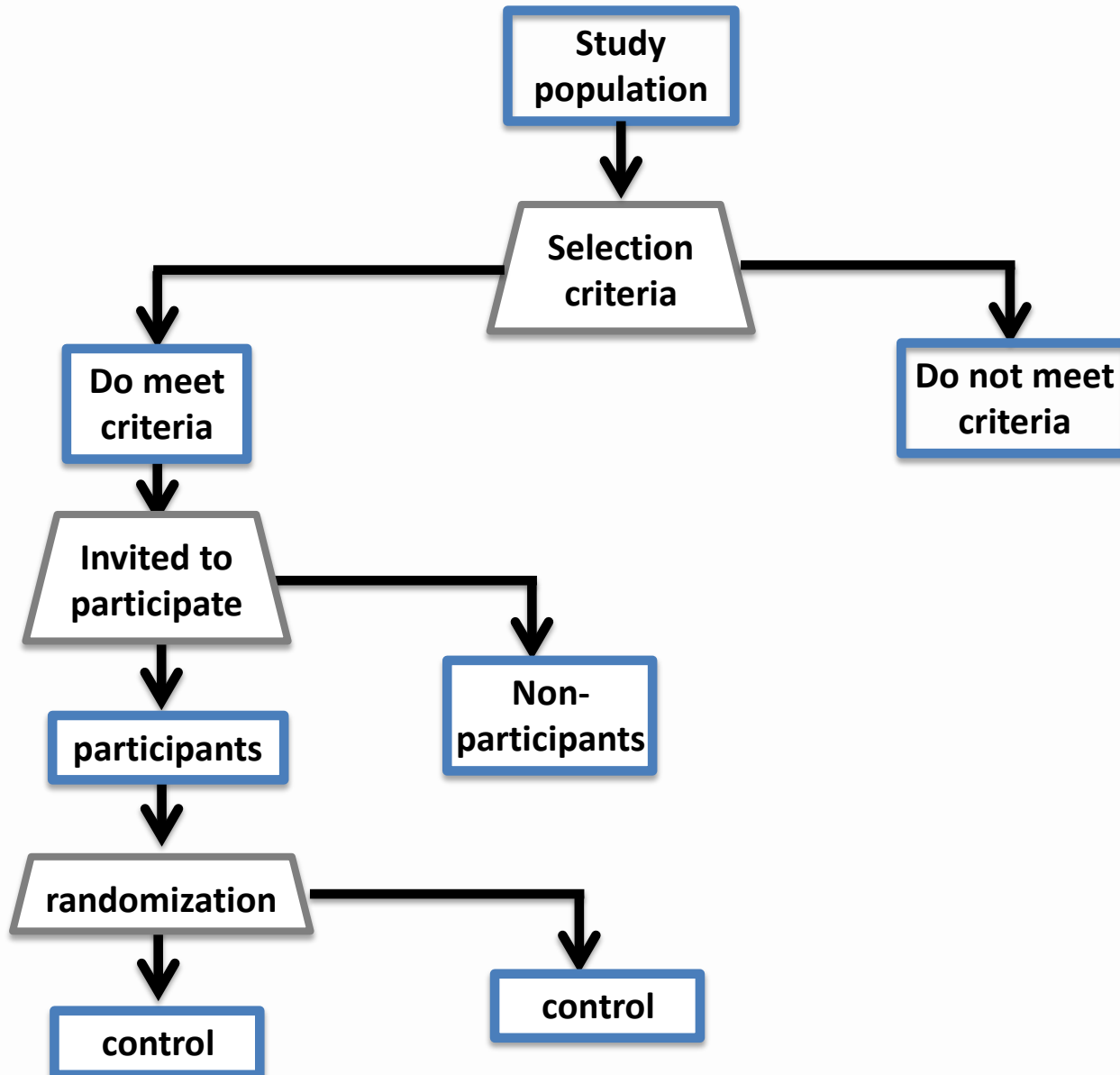
PH101

Spring quarter 2019

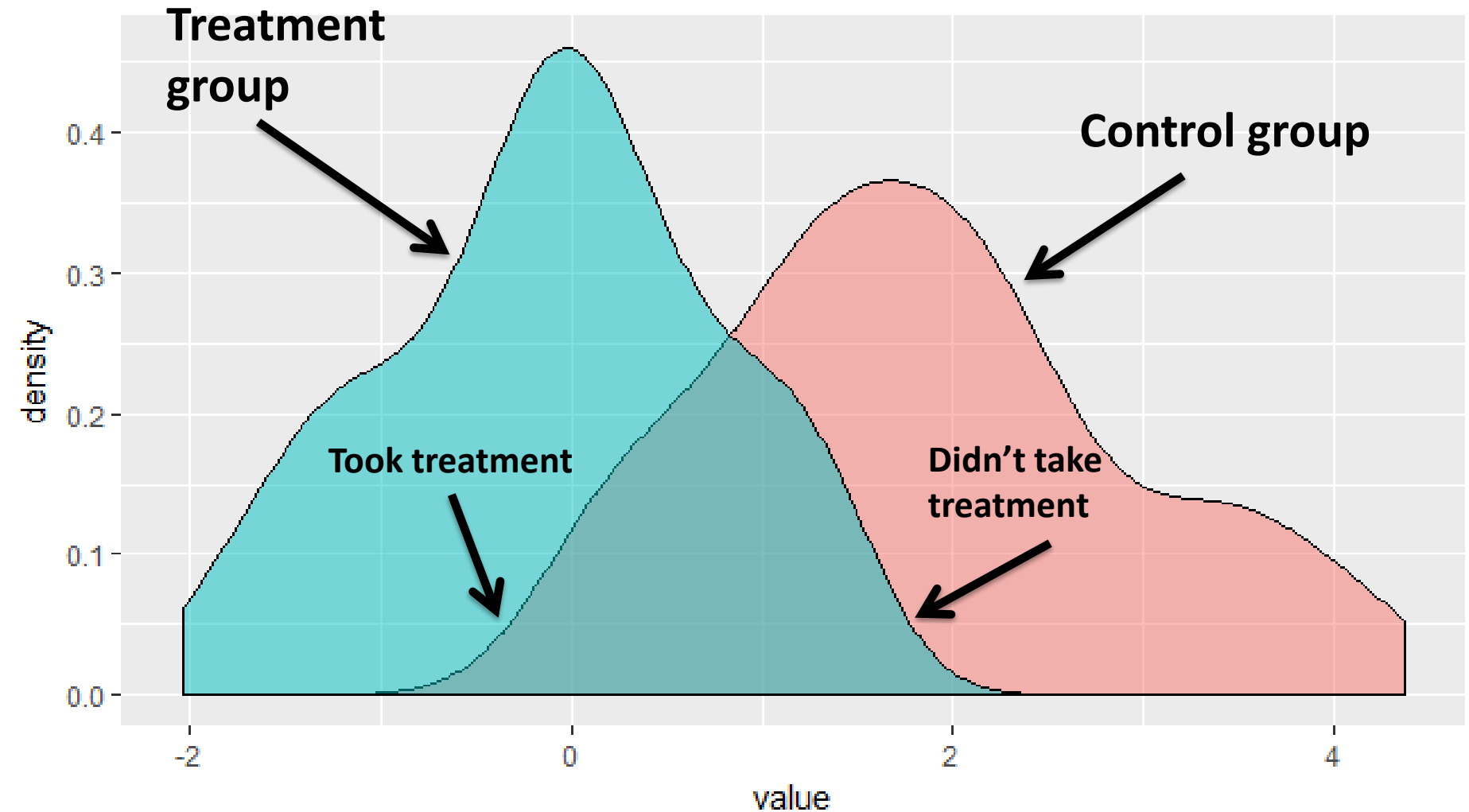
Lecture hall: PCB 1100

RCTs





Noncompliance



When should a trial be conducted?

- Rationale for an effect
- Uncertainty about whether or not the treatment really works (equipoise)
- A testable, falsifiable hypothesis
- It is reasonable to think that risks are smaller than benefits

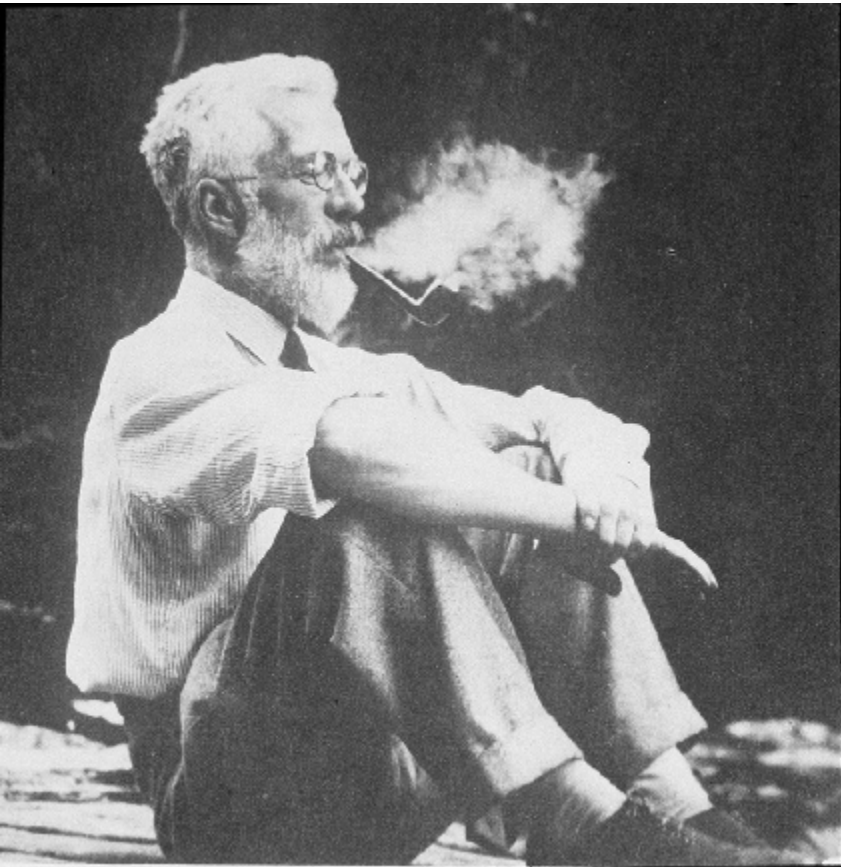
Stopping rules

- Undue risk
 - Severe adverse events
- Treatment is extremely effective
 - Should provide to the control group as well
- Continuing completely ineffective treatment

Sample size needed (power analysis)

Sample size

- Endpoints are frequently measured as events per person-time
- Sample size estimates will then estimate the necessary person-time required to detect a difference in rates between intervention and control
- A necessary sample size at enrollment is calculated, accounting for expected loss to follow up

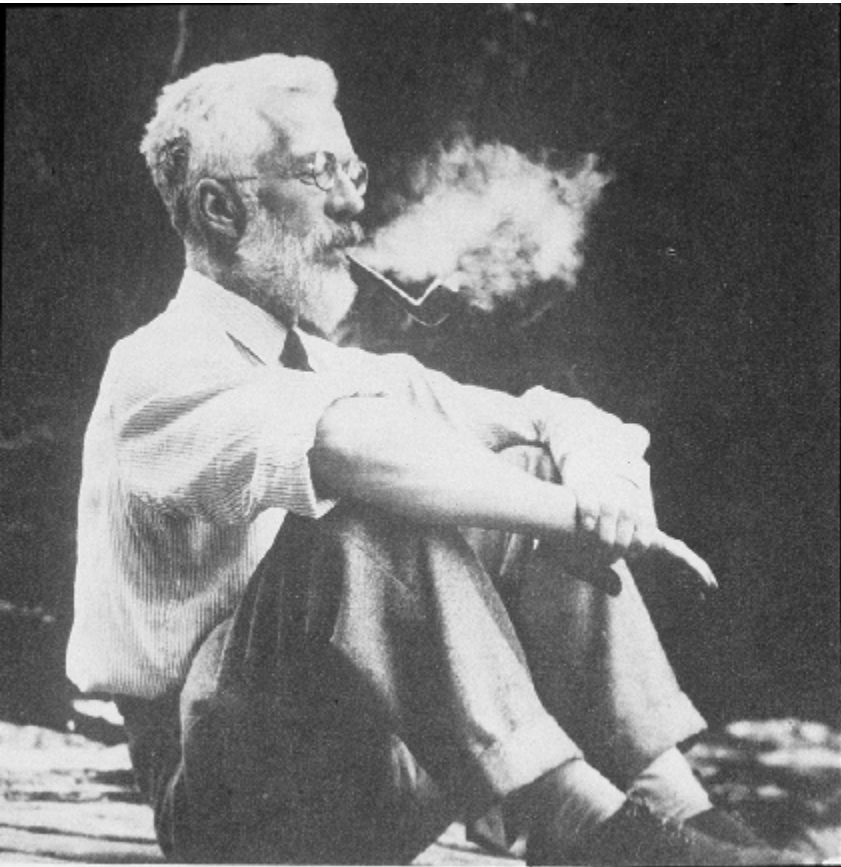


Ronald Fisher (1956)

$$H_0: \mu_1 = \mu_2$$

$$H_a: \mu_1 > \mu_2$$

$$H_a: \mu_1 < \mu_2$$



Ronald Fisher (1956)

$$p < 0.05$$

		reality	
		treatments are same	treatments are different
Conclusions	we conclude treatments are the same	correct	Type II error β
	we conclude treatments are different	Type I error α	correct ($1-\beta$)

α : Probability of finding a difference between treatments, when there really is none

β : Probability of finding no difference between treatments, when there really is one

power: $(1 - \beta)$ = Probability of detecting a difference, when the difference is real

Sample size needed (power analysis)

Must first specify:

1. How big of a difference to detect
2. Estimate of response (rate) in one group
3. Level of statistical significance
4. Value of power desired
5. Whether the test should be one- or two-sided

RCT results

Efficacy

- Efficacy: does the intervention work under ideal conditions
- Effectiveness: does the intervention work under normal conditions

This is a bit of a continuum.

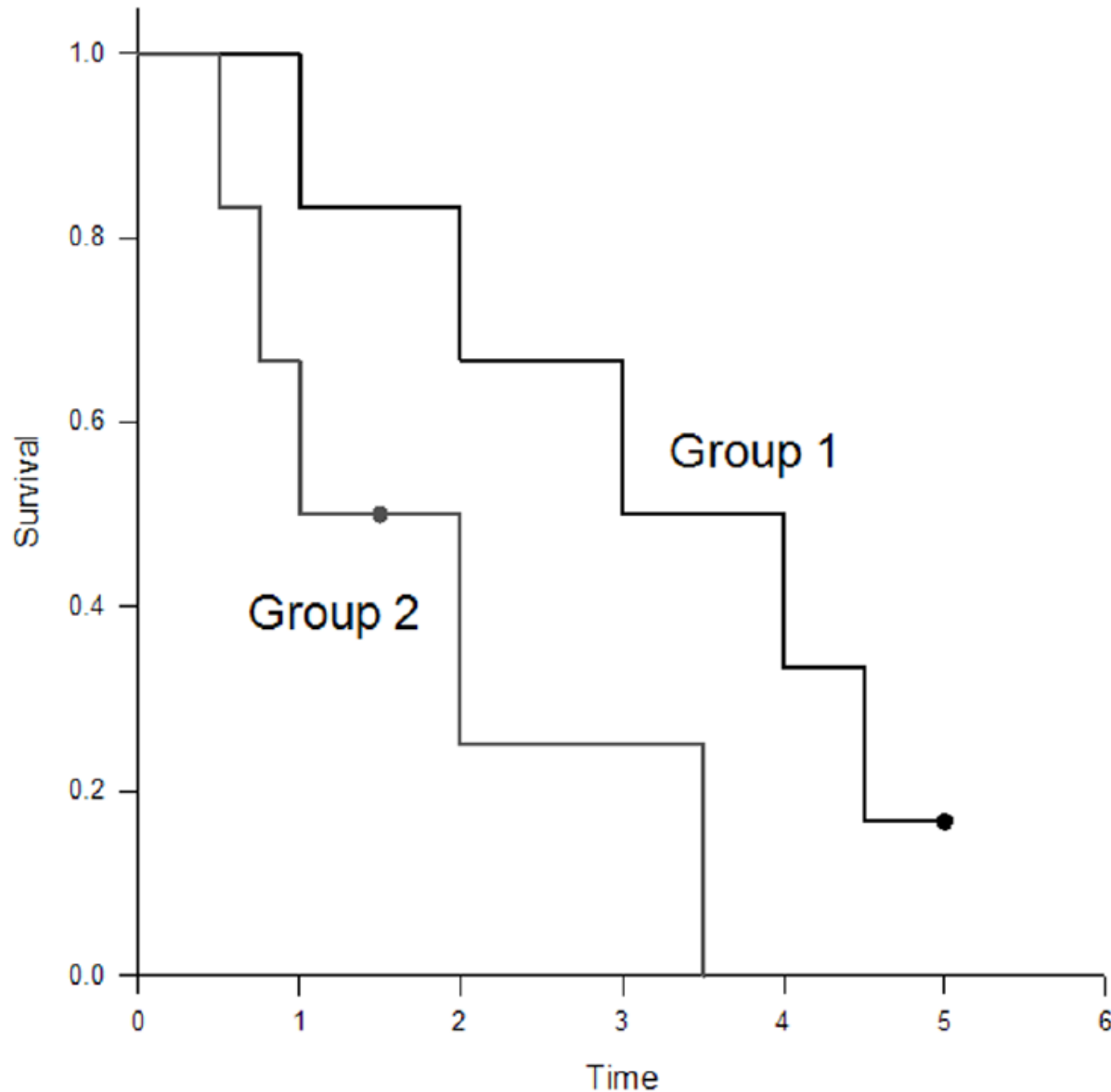
Efficacy

	Efficacy study	Effectiveness study
Question	Does the intervention work under ideal circumstance?	Does the intervention work in real-world practice?
Setting	Resource-intensive 'ideal setting'	Real-world everyday clinical setting
Study population	Highly selected, homogenous population Several exclusion criteria	Heterogeneous population Few to no exclusion criteria
Providers	Highly experienced and trained	Representative usual providers
Intervention	Strictly enforced and standardized No concurrent interventions	Applied with flexibility Concurrent interventions and cross-over permitted

Comparing groups

- Can use standard epidemiological measures. Usually accounting for person-time.
 - Incidence rate
 - Mortality rate
 - Survival curves

Kaplan-Meier Curve



Efficacy

$$\frac{(\text{rate in those with placebo}) - (\text{rate in those with treatment})}{\text{rate in those who received placebo}}$$

Efficacy

We are doing a clinical trial for a new rabies vaccine. We have selected participants from a colony near the Isle of Dogs, where ravenous canines who have acquired rabies infections are highly prevalent. All of the participants are runners and as a result of their behavior and their environment, they have a high risk of being infected with rabies. Half of the participants received the new vaccine whereas the other half received a placebo. Those who received the new vaccine had an incidence rate of 200 per 1000 per year while those with the placebo had an incidence rate of 500 per 1000 per year.

$$\frac{(\text{rate in those with placebo}) - (\text{rate in those with treatment})}{\text{rate in those who received placebo}}$$

NNT

NNT (number that need to be treated) to prevent 1 adverse outcome (such as death)

$$\frac{1}{(\text{rate in untreated group}) - (\text{rate in treated group})}$$

NNH (number needed to harm): for every
NNH individuals treated, one will be
“harmed”

RCT interpretation

- Remember that well-managed RCTs have good internal validity
 - For the population being studied, we can be relatively sure that causal associations are real
- Conversely, we need to think about how representative that population was with regard to other populations
 - Frequently have poor or questionable external validity

RCT interpretation

- Clinical trials have major implications
- Major global, international and national policies are based on RCT results
- They have implications for life and death situations
 - Not just for individuals but also for populations

Four phases in testing new drugs

Phase 1 trials

- Generally small (< 100 sample size)
- Determine safety and evidence of an effect

Phase 2 trials

- Larger than Phase 1 (100 – 200)
- Assess safety, acceptability/tolerance and effective dose (amount and frequency of dosing needed to be effective)

Phase 3 trials

- Larger sample size still (500+)
- Assess efficacy, acceptability, side effects and complications
- Submission for new drug approval (for example to the FDA or WHO)

Phase 4 trials

- Done in several 1000 volunteers
- Done after a new drug has been approved
- Post marketing trials in the general population
- Not a RCT

How we get new drugs (U.S.A.)

- Submit data (about toxicity, etc.) and proposal to FDA
- Phase 1 studies, usually in healthy volunteers, to determine potential side effects, metabolism, excretion (usually takes several months)
- Phase 2 begins to assess effectiveness in people who have the disease/condition (up to 2 years)
- Meetings between FDA and research team to assess the best approach for a Phase 3 trial
- Phase 3 is larger, assess proper dosing, combination therapies, and continues to look at safety and effectiveness (1 to 4 years)
- Afterwards the FDA may approve the drug and Phase 4 studies can be conducted in the general population (at least 2 years)
- Entire process takes on average 10 years (and several billion dollars)

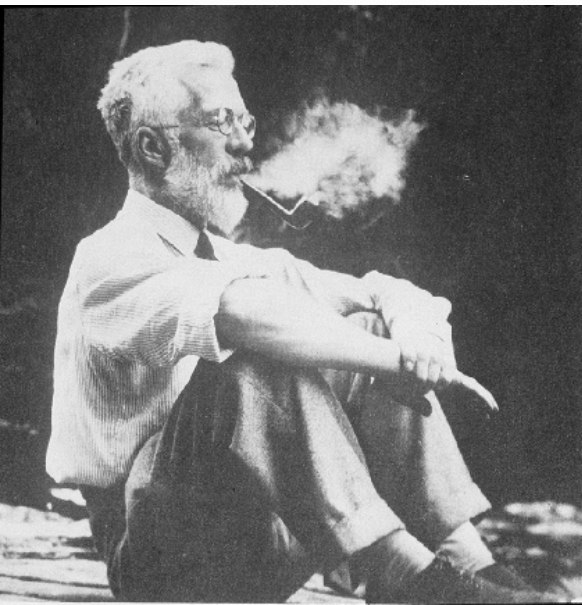
RCT and ethics

When is it unethical to randomize?

- Known effective treatment
- Personal choice
 - contraceptive forms wouldn't be ethical
- Risks of new treatment likely to exceed risks of new treatment

Trial registration

- Registration at beginning
 - <https://clinicaltrials.gov/>
- Publication bias



$$p \geq 0.05$$

How we get new drugs (U.S.A.)

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What kinds of diseases do RCTs focus on?

Who benefits most from most RCTs?

- Based on need or severity of disease?
- Economics
- Ones that pharmaceutical or other medical companies think will be cost effective
- Otherwise, we have philanthropists and governments

Paradox

- The RCT is our gold standard
- If we have a treatment (e.g. drug) that we believe works really well, we cannot use it in a RCT.
 - Meaning, we have no real way to prove that it works really well...
 - Or do we?

Who is OK to study?

- What about pregnant women?
- What about children?



Safety of artemisinins in first trimester of prospectively followed pregnancies: an observational study



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This online publication has
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The corrected version first
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infection on April 18, 2016

See [Comment](#) page 513

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Summary

Background Artemisinins, the most effective antimalarials available, are not recommended for falciparum malaria during the first trimester of pregnancy because of safety concerns. Therefore, quinine is used despite its poor effectiveness. Assessing artemisinin safety requires weighing the risks of malaria and its treatment. We aimed to assess the effect of first-trimester malaria and artemisinin treatment on miscarriage and major congenital malformations.

Methods In this observational study, we assessed data from antenatal clinics on the Thai–Myanmar border between Jan 1, 1994, and Dec 31, 2013. We included women who presented to antenatal clinics during their first trimester with a viable fetus. Women were screened for malaria, and data on malaria, antimalarial treatment, and birth outcomes were collected. The relationship between artemisinin treatments (artesunate, dihydroartemisinin, or artemether) and miscarriage or malformation was assessed using Cox regression with left-truncation and time-varying exposures.

Findings Of 55 636 pregnancies registered between 1994 and 2013, 25 485 pregnancies were analysed for first-trimester malaria and miscarriage, in which 2558 (10%) had first-trimester malaria. The hazard of miscarriage increased 1·61-fold after an initial first-trimester falciparum episode (95% CI 1·32–1·97; $p < 0·0001$), 3·24-fold following falciparum recurrence (2·24–4·68; $p < 0·0001$), and 2·44-fold (1·01–5·88; $p = 0·0473$) following recurrent symptomatic vivax malaria. No difference was noted in miscarriage in first-line falciparum treatments with artemisinin ($n = 183$) versus quinine ($n = 842$; HR 0·78 [95% CI 0·45–1·34]; $p = 0·3645$) or in risk of major congenital malformations (two [2%] of 109 [95% CI 0·22–6·47] versus eight (1%) of 641 [0·54–2·44], respectively).

Interpretation First-trimester falciparum and vivax malaria both increase the risk of miscarriage. We noted no evidence of an increased risk of miscarriage or of major congenital malformations associated with first-line treatment with an artemisinin derivative compared with quinine. In view of the low efficacy of quinine and wide availability of highly effective artemisinin-based combination therapies, it is time to reconsider first-trimester antimalarial treatment recommendations.

Lecture summary

- Steps in RCTs
- Power analysis
- Quantifying outcomes
- Phases of trials
- RCT ethics

- Ebola scenario
 - <https://www.youtube.com/watch?v=5Kvo9PIIfKI>
 - <https://www.youtube.com/watch?v=5Hj4akvDNSs>
- Ebola clinical trials
 - <https://www.youtube.com/watch?v=6lapce9MkqU>
- TB clinical trials
 - <https://www.youtube.com/watch?v=hCMY1Pf9PKg>

An example of an RCT from the literature

An example of a RCT

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Single-Dose Perinatal Nevirapine plus Standard Zidovudine to Prevent Mother-to-Child Transmission of HIV-1 in Thailand

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Scientific papers

- Abstract
- Background/introduction
- Methods (data and analysis)
- Results
- Discussion

hypothesis

BACKGROUND

Although zidovudine prophylaxis decreases the rate of transmission of the human immunodeficiency virus (HIV) type 1 substantially, a large number of infants still become infected. We hypothesized that the administration, in addition to zidovudine, of a single dose of oral nevirapine to mothers during labor and to neonates would further reduce transmission of HIV.

METHODS

TRIAL DESIGN

We conducted a multicenter, phase 3, double-blind, randomized, placebo-controlled trial. The primary objective was to assess the safety and efficacy of a single dose of nevirapine administered to women at the onset of labor and given to infants between 48 and 72 hours after birth, added to zidovudine prophylaxis, for the prevention of mother-to-child transmission of HIV type 1. A secondary objective was to evaluate the incremental effect of the administration of perinatal nevirapine to newborns.

The ethics committees of the Thai Ministry of Public Health, Chiang Mai University, and the Harvard School of Public Health approved the protocol used in the study, including the amendments. All study sites complied with regulations of the Department of Health and Human Services for the protection of human research subjects.

PATIENTS

Eligible subjects were pregnant women participating in the national program of voluntary counseling and testing who were receiving zidovudine prophylaxis (starting at 28 weeks' gestation or as soon as possible thereafter) at any of 37 study sites in Thailand. The subjects were enrolled between

$\mu\text{mol per liter}$). Exclusion criteria included a maternal or fetal condition or a concomitant treatment that contraindicated treatment with zidovudine or nevirapine, oligohydramnios, unexplained polyhydramnios or in utero anemia, or a medical condition that required immediate use of highly active antiretroviral therapy. Open-label nevirapine was available

Pre-specified follow up times and frequencies

Until delivery, the women in the study had an obstetrical examination every two weeks; every other week, blood was drawn for hematologic, virologic, and biochemical testing. Adherence to zidovudine therapy was assessed at each visit by counting pills. After delivery, the women were seen at 10 days, 6 weeks, and 4 months for a physical examination and for hematologic and virologic monitoring. They were referred to an internist for further follow-up.

Infants were examined at birth, and follow-up visits were scheduled at 10 days (for measurement of hematocrit and alanine aminotransferase levels), 6 weeks (for hematologic tests), and 4, 6, 9, and 12 months. At each visit, a supply of powdered formula

randomization

TREATMENT

Women were randomly assigned to one of three treatment groups. In the nevirapine–nevirapine group, women received one dose of oral nevirapine (200 mg) at the onset of labor and neonates received nevirapine oral suspension (6-mg fixed dose, 0.6 ml) between 48 and 72 hours after birth. In the placebo–placebo group, women received placebo at the onset of labor and neonates received placebo between 48 and 72 hours after birth. In the nevirapine–placebo group, women received one dose of oral nevirapine (200 mg) at the onset of labor and neonates received placebo between 48 and 72 hours after birth.

Pre-specified endpoint(s)

PRIMARY END POINT

Infants were considered to be infected with HIV if the results of the PCR test were positive in blood obtained on two separate occasions, and infants were considered to be uninfected if the test results were negative on two occasions after one month of age.¹¹ Infants who did not meet this definition were evaluated and classified as infected (six infants) or uninfected (three infants) by a clinician and a virologist before unblinding. In twins, infection in one or both was counted as one transmission.

Analysis type

STATISTICAL ANALYSIS

The study was designed primarily to test the superiority of the nevirapine–nevirapine regimen over the placebo–placebo regimen. We calculated that 484 mother–infant pairs were needed in each treatment group for a 0.05 one-sided type I error with 0.8 power, assuming a transmission rate of 8 percent in the placebo–placebo group and 4 percent in the nevirapine–nevirapine group. The nevirapine–placebo group was added in order to estimate, as a secondary objective, the proportion of overall transmission that was prevented by treating infants with nevirapine. Assuming that 5 percent of the cases could not be evaluated, the initial target sample size was 1530.

Trial monitoring and stoppage

After the first interim analysis, on May 2, 2002, the independent data and safety monitoring committee recommended stopping enrollment in the placebo–placebo group. The trial design was modified, and the target sample size was increased to

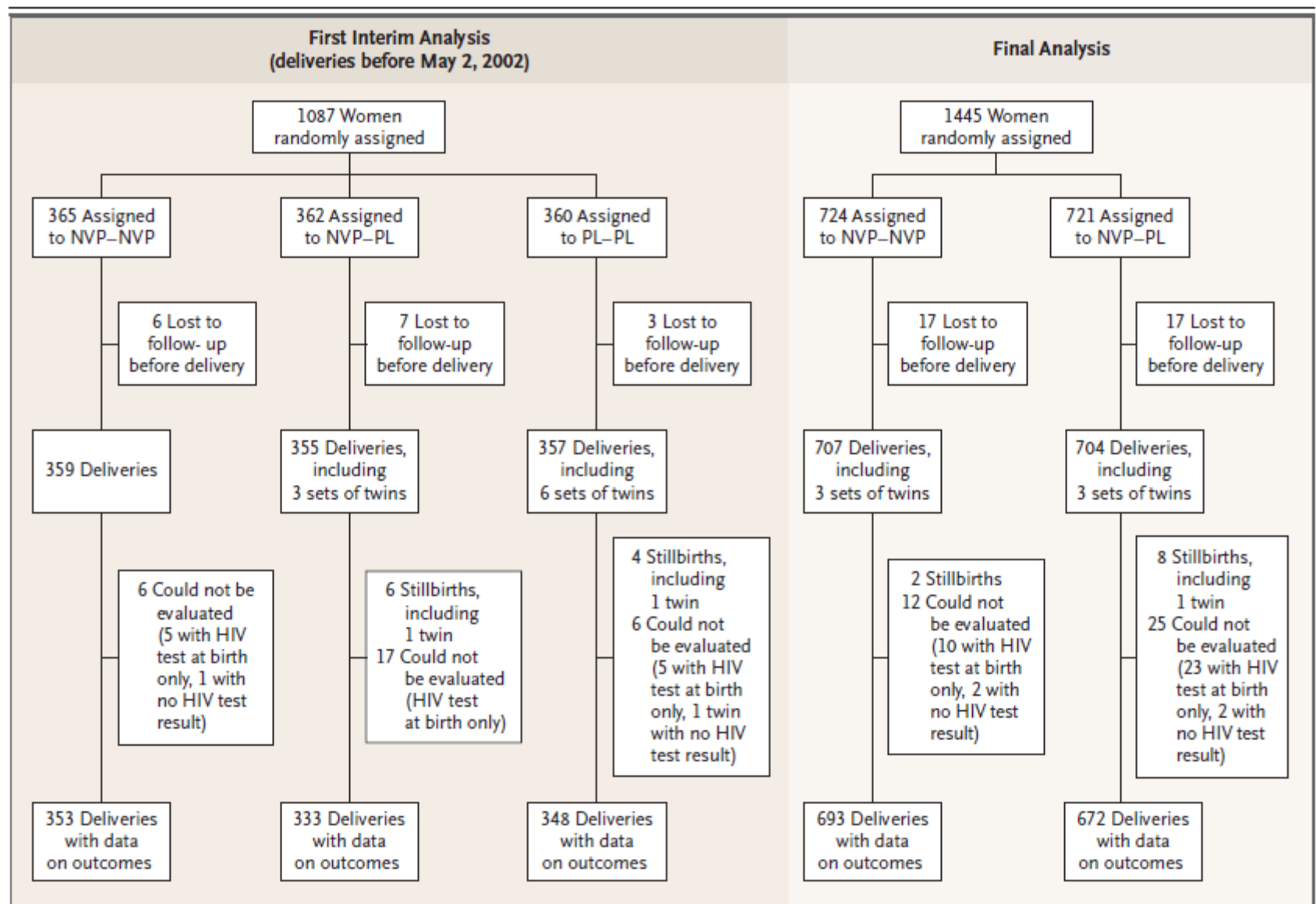


Figure 1. Treatment Assignment, Loss to Follow-up, and Outcome of Pregnancy.

Thirty-nine women assigned to the placebo–placebo group were excluded from the analyses, because they were given open-label nevirapine (NVP) after the first interim analysis. PL denotes placebo. Delivery of twins counted as only one delivery.

results

Table 3. Estimates of the Rate of Transmission of HIV or Death at Six Months, According to Treatment Assignment.*

Variable	Interim Analysis			Final Analysis	
	NVP–NVP Group	NVP–PL Group	PL–PL Group	NVP–NVP Group	NVP–PL Group
No. of infants at risk	359	350	354	705	697
No. of transmissions overall	4	7	22	14	19
Infants who died by 6 months (no.)					
HIV-positive	0	0	2	1	2
HIV-negative	0	0	1	0	0
Indeterminate HIV status with severe congenital malformations	0	2	0	0	6
Other indeterminate HIV status	1	1	2	1	2
Total no. of deaths at six months†	1	3	5	2	10
No. of transmissions or deaths overall	5	10	25	15	27
Rate (%)‡	1.4±0.6	3.0±0.9	7.2±1.4	2.2±0.6	4.0±0.8
No. of transmissions or deaths excluding infants with congenital malformations and HIV-negative infants	5	8	24	15	21
Rate (%)‡	1.4±0.6	2.5±0.8	6.9±1.4	2.2±0.6	3.1±0.7

bly related to nevirapine even in the placebo–placebo group, since classification was performed by persons blinded to treatment assignment. Nineteen infants died within six months after birth (Table 3).

DISCUSSION

This study demonstrates the high efficacy of adding a single dose of nevirapine in the mother, with or without a dose in the infant, to oral zidovudine prophylaxis for the reduction of perinatal transmission of HIV. The observed reduction by 80 percent that led to the early interruption of enrollment in the placebo–placebo group was much higher than we had hypothesized when we designed the study. The transmission rate observed in the placebo–placebo group was consistent with rates observed in

other studies in which zidovudine prophylaxis was initiated at the beginning of the last trimester of pregnancy,^{1,19-21} in particular in our previous trial, which was performed in a similar population.⁵

Although the efficacy of a single maternal dose of nevirapine was declared statistically noninferior to that of a maternal dose plus an infant dose with the use of our predetermined criteria (2.5 percent as the upper limit of the one-sided 95 percent confidence interval for the difference between the observed rates of transmission), in fact, two doses appeared consistently better than one throughout our analysis (Table 4). Moreover, because the nevirapine–placebo group had a somewhat lower median viral load at baseline than the nevirapine–nevirapine group, the difference in transmission rates might be an underestimate. On the basis of these findings

Publishing bias

<https://www.youtube.com/watch?v=-RXrGLolgEc>