Ethical Issues in HIV Research: Remune and iPrEx

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My Journey

- 1993: Graduate from U. of Washington
- 1993-1997: Post-doc and Researcher at Harvard Biostat and AIDS Clinical Trials Group
- 1997 to present: Faculty at UCSF
- UCSF: based in a medical school
  biomedical focused campus of UC
  diverse collaborations and roles

Heady Stuff

- Be involved with high-impact work
  work that may change medical/public health practice, revolutionize a field
- Keep confidential highly important study results ... for months or even years
- Be the first to know the results

Stressful Stuff

- High impact work comes with tremendous controversy and scrutiny: standards for accuracy couldn't be higher
- Keeping secrets complicates lots of interactions
- You will have to deliver news of a study
- Often this will be disappointing news
  even very disappointing news

Ethical/Collegial Tension

- Biostatistics: collaborative profession
- What makes a sought after biostatistician? *knowledge, communication, collegiality*
- May be praised for being agreeable even if not upholding high scientific standards
- May be disdained by colleagues for upholding high standards

central ethical tension in biostatistics

My Talk

- Introduce you to some real-life situations
- Explore the ethical dilemmas
- Examine barriers to acting ethically
- Highlight pressures to be accurate
- Discuss special role of biostatisticians

Self-Serving Bias

Dana and Lowenstein, JAMA 2003

- People can't remain objective when they have a vested interest in conclusion
- Bias is
  - unintentional
  - unconscious
  - affects how people weigh evidence/ arguments

The Remune Story

Immune Response Corporation (IRC)

- Formed 1987 by Dr. Jonas Salk
  legendary polio vaccine researcher
- Product: killed HIV with envelope protein removed (Remune)
- Quickly abandoned as preventative vaccine
- Explored as therapeutic vaccine
  stimulate anti-HIV reaction

The Salk Name

Time Magazine, 1995

Salk and vaccine. the words somehow belong together-like Fleming and penicillin or Einstein and relativity. So when Dr. Jonas Salk, the developer of the first effective vaccine against polio, announced eight years ago that he was coming out of retirement to tackle AIDS, many people cheered-especially the growing numbers of patients infected with hiv. Who better to lead the charge against the current plague than the conqueror of an infamous childhood scourge?

Salk Vaccine

- Never fully accepted as mainstream treatment
- Suggestion that data overhyped
- Early work used unvalidated surrogates
- Immune based therapies very appealing
- Salk's name carried a lot of cache

AIDS Meeting

June 10, 1993, Berlin, SHERYL STOLBERG Los Angeles Times

Releasing long-awaited test results, polio pioneer Jonas Salk announced Wednesday that his experimental AIDS vaccine appears to boost the immune systems of people infected with the human immunodeficiency virus. But his work met with immediate skepticism from other scientists gathered here at the Ninth International Conference on AIDS.

"I'm less than enthusiastic," said David Ho of the Aaron Diamond AIDS Research Institute in New York. Robin Weiss, the renowned British virologist, said of the presentation by Salk's collaborators: "It was a dog-and-pony show."

Vaccinated patients developed more antibodies to a core protein of HIV. They also showed stable levels of "viral burden"--the amount of virus in the blood--while unvaccinated patients showed an increase. And their CD4 cells--the immune system cells that are the main targets of HIV--demonstrated improved function.

FDA Advisory Committee

- Approved 806 trial in February 1995
- Split decision 6-3 (1 abstention)
- Against -- lack of compelling data
- For -- rigorous data may finally settle efficacy

Skepticism

Last week an expert advisory panel to the Food and Drug Administration recommended that the agency allow Salk to test his AIDS vaccine on 5,000 volunteers. If the FDA agrees, Salk's preparation would be the first AIDS vaccine to undergo a large-scale trial in the U.S.
Yet the endorsement was hardly ringing, because the early evidence of the vaccine's worth, from tests involving small numbers of patients, was far from compelling. The panel's vote split 6 to 3 in favor of further testing, with one member undecided. "I am not all that excited about the data I've seen," admits committee chairman Dr. Stanley Lemon of the University of North Carolina. "But I would be thrilled to be proven wrong

But such a policy is not without pitfalls. If patients participate in the trial of an ineffective treatment, they may not get a chance to try better therapies that come along later. That is the reason the FDA traditionally insists on significant evidence of effectiveness before approving large trials. "By lowering the standards we have increased the level of confusion about how to treat people with AIDS," says Dr. Deborah Cotton of Massachusetts General Hospital.

Political Pressure

Then why did the FDA panel vote for wider testing? Clearly, Salk himself was a big selling point. "He has a reputation among some scientists as a god," says one top AIDS researcher. "He's a powerful advocate, and they find it very hard to turn him down." The committee may also have had a hard time saying no to the AIDS patients who participated in the early pilot programs. They fear that if the FDA does not expand the trial, they will no longer receive the shots. And many are convinced that the treatments are helping. Mike Slattery of Los Angeles, who began receiving Salk's vaccine in 1988, cites lab tests showing that his immune system is deteriorating more slowly than might otherwise be expected. "I'm going to live 10 years longer because of this," he says. "This may provide a bridge so that I will be alive when effective treatments arrive."

Stephen W. Lagakos

- Prof. of Biostatistics, Harvard ’78 to ’09
- Skilled collaborator
- Leader in AIDS Clinical Trials Group
- PI of statistical center for ACTG
- Generous mentor

Lagakos/Kahn

- Previously collaborated on HIV trials
  ACTG 116B
- Developed an academic/industry hybrid
- Would provide outside experienced expertise for industry
- Taken up by 2 small California companies
  IRC and Gilead
- Not 100% clear on the attraction

Protocol 806

- Double blinded IFA controlled
- Flexible background ART therapy
- Outcome: death/clinical progression
- 90% power to detect HR of 0.50
- ~240 events desired
- RNA every 24 weeks
  10% cohort had it every 12 weeks

Changes in Trial Environment

- Enrolled 3/96 to 5/97
- Early 1997, ACTG 320 established 3 drug therapy as superior
- During that time HAART comes into wide use
- Concern about event rates
  - expansion of endpoint definition
  - inclusion of HIV RNA

DSMB Issues

- Monitored by Lan-DeMets with O'Brien Fleming use function -- 3 equally spaced efficacy analyses
- No formal guidance mentioned for futility
- Met for efficacy 6/98 and 5/99
- May 15, 1999 recommend termination of trial -- lack of efficacy and futility
- IRC notified on May 17, study terminated can't find press release

ICAAC 1999

A Randomized, Placebo Controlled Multicenter Study of Remune in Subjects with 300-550 CD4 Cells and Unrestricted Anti-Retroviral Treatments.

KAHN J, LAGAKOS S, MAYER K, MURRAY H; Interscience Conference on Antimicrobial Agents and Chemotherapy.

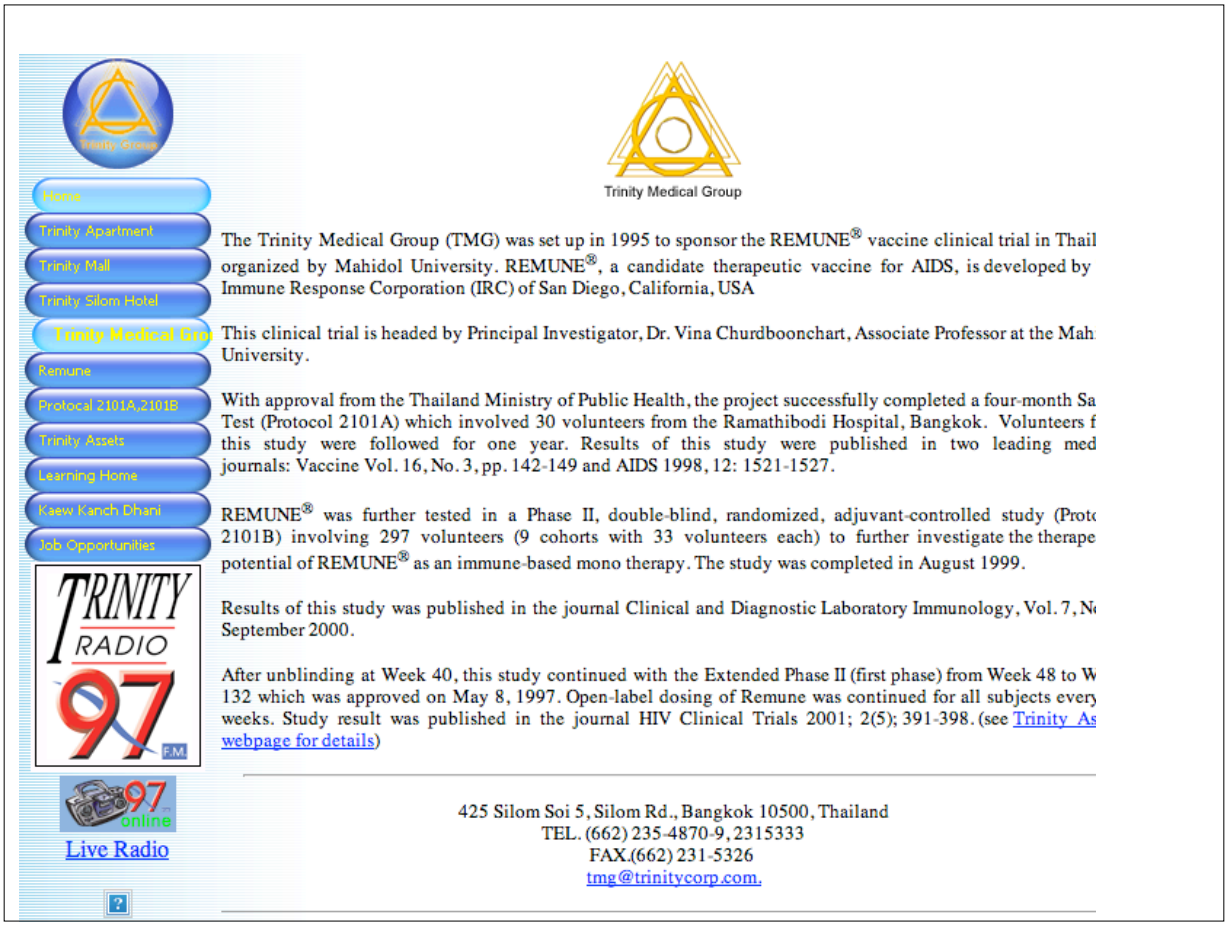
Abstr Intersci Conf Antimicrob Agents Chemother Intersci Conf Antimicrob Agents Chemother. 1999 Sep 26-29; 39: 18 (abstract no. LB-21).
Univ. of California, San Francisco, San Francisco, CA
INTRODUCTION: Injections of Remune, an envelope depleted HIV protein matrix complexed with Incomplete Freund's Adjuvant (IFA), induces lymphocyte proliferation (LP) to core proteins. In previous studies Remune was associated with control of HIV-1 RNA.METHODS: We conducted a placebo controlled 77 center study randomizing 2527 subjects to Remune or IFA placebo. The primary efficacy endpoint was clinical progression free survival; secondary endpoints included the average change from baseline (AUCB) for HIV-1 RNA (VL) and CD4 cells. Injections with Remune or IFA placebo occurred every 12 weeks.RESULTS: Beginning in 1997 we recruited 2527 subjects; 1262 randomized to Remune and 1265 randomized to IFA. The average follow-up time was 88.7 weeks. The annualized lost to follow-up was 8%. Treatment groups were well balanced by common baseline characteristics. Clinical AEs associated with Remune were local reactions. Thus far 90 patients experienced clinical progression: 44 patients randomized to Remune and 46 to placebo (P=0.75). The DSMB recommended stopping the study due to the low event rate and lack of difference between the two groups. Baseline VL and CD4 cells were 3.1 log10 and 418/micro-L. Preliminary laboratory studies of VL from 1,567 of the 2527 subjects showed no statistically significant difference between the groups; and at week 48, the CD4 AUCB showed a 16 cell difference in favor of the Remune group (P<0.01). LP to HIV and p24 was observed in 45% and 34% for the Remune group and <1% among the placebo group.CONCLUSIONS: The overall progression rate was 2.1 events per 100 person years of follow-up. Remune was immunogenic and associated with no effect on clinical progression. Preliminary data demonstrate a mild increase in CD4 count, no VL effect was discerned.

Thai Study

- In 1995, a wealthy Thai couple invested in IRC -- $5 Million
- Their company -- Trinity Medical Group
- Investor would serve as PI of the study *faculty at Mahidol University*
- Would run Thai-based trials of Remune
- Would have exclusive marketing rights in Asia for Remune

Warning Signs

- Financial conflict of interest
  unknown at the time
- Not an experienced PI
- Tended to operate in a close knit circle of mutually beneficial relationships



My involvement

- I was not involved in 806
- Involved in setting up that Thai study
- Developed protocol, data analysis plan, randomization list and case report forms
- Made 3 trips to Thailand from Fall 1995 to March 1996
- Soyeon Kim takes over role in 1997
- March 1999, Thai DSMB meets
  PI and IRC try to get me involved

Thai Study Dispute

- Study written up without statisticians
  Kim or Lagakos
- Analysis did not follow analysis plan
- Examine large number of secondary endpoints
- Emphasize positive one disproportionately
- Paper published just prior to JAMA
  fits a pattern by IRC

Points of Discussion

Crux of the Dispute

- Overall tone of paper
- Emphasis on HIV RNA data
- Plausibility of IRC's RNA analysis
- Access to complete data

Evaluating IRC Arguments

- Clinical endpoint data not meaningful
  - event rates are too low
  - HAART muddies the waters
- Kahn is suppressing data
  - favorable RNA trends
  - lymphocyte proliferation, subgroups
- Kahn is excluding investigators

Ethical Principles in Tension

- Respect for colleagues
  how to include investigators
- Social responsibility
  duty to share results
- Respect for participants
  informing them of results and how it's done
- Responsible publication
  completeness, accuracy, timeliness

My Questions

With the benefit of hindsight

- With the benefit of hindsight
  - Would you do the trials?
  - How would you structure agreement?
  - How would you approach concomitant antivirals?
  - View of the viral load data
  - Would you have contacted investigators?

Publication Issues

- Shifting endpoint
  definition, evaluation or relative importance
- Shifting analysis techniques
- Emphasis on subgroups
- Result interpretations
- Relative importance of conflicting results

Recent Positive Experience of Mine

The NEW ENGLAND JOURNAL of MEDICINE

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Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

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ABSTRACT

BACKGROUND

Antiretroviral chemoprophylaxis before exposure is a promising approach for the prevention of human immunodeficiency virus (HIV) acquisition.

METHODS

We randomly assigned 2499 HIV-seronegative men or transgender women who have sex with men to receive a combination of two oral antiretroviral drugs, emtricitabine and tenofovir disoproxil fumarate (FTC–TDF), or placebo once daily. All subjects received HIV testing, risk-reduction counseling, condoms, and management of sexually transmitted infections.

RESULTS

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Grant at the J. David Gladstone Institutes, University of California at San Francisco, 1650 Owens St., San Francisco, CA, 94158, or at robert.grant@ucsf.edu.

*Other members of the Preexposure Prophylaxis Initiative (iPrEx) study team are listed in the Supplementary Appendix, available at NEJM.org.

This article (10.1056/NEJMoa1011205)

iPrEx Study

- Randomized placebo controlled study
- Funded by NIH and Gate Foundation
- Daily anti-viral pill to prevent HIV infection
  sexually active men who have sex w/ men
- 2,499 participants, 5 countries
- 600, 000 case report forms
- ~ $44 million dollar study

Plan for Reporting

- Visits through 1 May 2010
- Data analyzed in 3 weeks
- Database locked in summer 2010
  took until 20 August 2010
- Study continues through Nov 2010
- Rapidly produce publication
  confidential until embargo lifts with manuscript publication

Accuracy

- Get involved in data management
- Settle on analysis template
- Begin programing early
- Produce automatic output
- Independent programming

Confidentiality

- Don't. Say. Anything.
- Avoid situations which threaten confidentiality
- Avoid printing, shred, close doors
- Don't allude to the fact that you know confidential information

Study Result

HIV infection

- Primary outcome: HIV infection
- 110 infections through 1 May 2010
  10 people infected at enrollment
- 64 on placebo 36 on FTC/TDF
  8/10 baseline infections on placebo
- hazard ratio: 0.56, 95% CI (0.37 to 0.85)
- Efficacy: 44%, 95% CI (15% to 63%)

Baseline Infections

- Unavoidable lag in detecting HIV infection
- Protocol very clear that baseline infections excluded
- Baseline infections:
  8 on placebo, 2 on FTC/TDF, p=0.06
- Baseline infections only detected if person tests positive during FU
- Change or efficacy?

Null Hypothesis

- Power to rule out 30% efficacy if true efficacy was 60% or higher
- P=0.15 to rule out null of 30%
- P=0.005 to rule out null of 0%
- How much to emphasize the two findings?
- Put P=0.15 in abstract?

Drug Level Analysis

- Tested for drug in active arm HIV+ and sample of HIV-
- Drug detected in 3/31 cases and 22/43 controls
- Conditional logistic regression: OR = 12.7, 92% reduction in risk due to detectable drug
- How to present this analysis in a nuanced way? Should it go in the abstract?

Biostatistics and Ethics

- You will play pivotal role in medical research
- Looked to uphold high standards
  can be a lonely role
- People close to research become conflicted
- Mitigate conflicts where you can
- Insist on pre-specification
  analyses, standards
- Right to publish, access to data