Fighting AIDS with Research: Microbicides, Vaccines, Pre-exposure Prophylaxis and Gene Therapy

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Positive Living 14  Saturday, March 12, 2011
• Introduction
• Basic Principles
• Current Research & Issues
• Community’s Role
Two Big Questions:

• How does research affect us?
• How can we affect research?
NIAID Agenda: Controlling & Ending the Pandemic

- Aggressively seek, test, and treat positive individuals
- “Cure” existing infections
- Prevent new infections (including new prevention technologies)
What is a Clinical Trial?

A clinical trial is a scientifically planned experiment that involves volunteers (patients)
Is it a “real” clinical trial?

- Conducted by reputable entity
- Peer reviewed
- Published in a major scientific journal
Fundamental Concepts

- **Control**: comparison
- **Placebo**: “sugar pill”
- **Double-blinded**: neither participant nor provider knows
- **Randomized**: assigned by chance, as if by toss of the coin
Progression of Research

- **Laboratory**, then **animal** studies
- **Phase I** - A few people try drug for safety/tolerance
- **Phase II** – Hundreds of people; continue to evaluate safety and begin to determine dosage and efficacy
- **Phase III** – Involves larger numbers of people; verify safety and effectiveness
- **Phase IV** – Post approval / marketing
When Things Go Wrong - Lessons from History

- How does this affect community?
- How does this affect trials?
- What happens when a community does not participate?
The Safety Net

- Regulations enforced by the FDA, OHRP and other agencies
- Institutional Review Boards
- Data Safety and Monitoring Boards
- Community Vigilance
Other Protections

- Voluntary participation
- Protocol design - “safety valves”
- Informed consent
Informed Consent in a Nutshell

• YES, this is research
• There may be risks
• There may be benefits
• There are alternatives to participating
• Confidentiality will be handled . . .
• Reimbursement / compensation is . . .
• If you have a question or problem, call . . .
• The decision is YOURS
Eligibility

Inclusion & Exclusion Criteria
- rules about who can and cannot participate
The Balancing Act

- Urgency vs. Safety
- Robustness (thoroughness) vs. cost
- Study size, length, complexity
- Risk is not a dirty word
Weighing the Results

- "n" – Number of participants
- Observational vs. Intervention
- Prospective vs. Retrospective
- Blinding, Randomization
- Primary vs. Secondary Objectives
- Confounding factors
- Corroborates existing knowledge?
- Sponsorship
Current Research: Good News

- Vaccine
- Vaginal Microbicide
- PrEP in MSM
- Gene therapy mimics Berlin patient?
Research Issues - Prevention

- Study size
- Risk identification
- Few endpoints
- Efficacy, partial efficacy, & effectiveness
- Lack of reliable incidence measure
Research Issues – Vaccine

- Correlates of protection
- Comparison arm
### Summary of Analyses

<table>
<thead>
<tr>
<th></th>
<th>ITT</th>
<th>mITT</th>
<th>PP</th>
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<tbody>
<tr>
<td>N (# subjects)</td>
<td>16,402</td>
<td>16,395</td>
<td>12,542</td>
</tr>
<tr>
<td>Person years</td>
<td>52,985</td>
<td>52,985</td>
<td>36,720</td>
</tr>
<tr>
<td>Vaccine/Placebo (event #)</td>
<td>56 / 76</td>
<td>51 / 74</td>
<td>36 / 50</td>
</tr>
<tr>
<td>Vaccine efficacy</td>
<td>26.4%</td>
<td>31.2%</td>
<td>26.2%</td>
</tr>
<tr>
<td>2-sided p value</td>
<td>0.08</td>
<td>0.04</td>
<td>0.16</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>-4.0, 47.9</td>
<td>1.1, 51.2</td>
<td>-13.3, 51.9</td>
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</tbody>
</table>

- Includes 5 vaccine and 2 placebo recipients who were HIV positive at baseline
- Decreased event numbers, lower precision
RV144 Thai Vax Trial in a Nutshell

- 16,402 participants, 60/40% M/F, age 18-30, "average" risk (3%)
- Low adverse events in both arms
- No effect on viral load or CD4 count
- Low number of seroconversions
- Mechanism of protection not apparent
- Higher efficacy associated with lower risk
- Short durability?

Proof of concept?
Current Issues – PrEP & ‘cides

- Cost, prioritization
- Adherence
- Resistance
- Interest / uptake
- Implementation
- Disinhibition
CAPRISA in a Nutshell

- Adherence – a challenge, dose effect seen
- Disinhibition – “no increase in HIV risk behavior”
- Side effects
  - Small increase in mild diarrhea
  - No kidney effects seen
  - No liver / Hep B effects seen
- Resistance:
  - None observed
# HIV infections & Women-years

<table>
<thead>
<tr>
<th></th>
<th>Tenofovir</th>
<th>Placebo</th>
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<tbody>
<tr>
<td># HIV infections</td>
<td>38</td>
<td>60</td>
</tr>
<tr>
<td>Women-years (# women)</td>
<td>680.6 (445)</td>
<td>660.7 (444)</td>
</tr>
</tbody>
</table>

**HIV incidence** (per 100 women-years)

<table>
<thead>
<tr>
<th></th>
<th>Tenofovir</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.6</td>
<td></td>
<td>9.1</td>
</tr>
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**Incidence rate ratio:** 0.61 (CI: 0.4 to 0.94);  $p = 0.017$

**39% lower HIV incidence in tenofovir gel group**

Quarraisha & Salim S Abdool Karim – IAS AIDS 2010 Vienna
iPrEx in a Nutshell

- **Adherence** – split: “nearly daily or not at all”
- **Disinhibition** – no significant differences in condom use, # of partners, high risk
- **Side effects**
  - Elevated creatine
  - Nausea
- **Resistence:**
  - 0 in true HIV negatives
  - 1 transmitted (placebo arm)
  - 2 acquired (treatment arm - acutely infected @ enrollment)
Efficacy (MITT) 44% (15-63%)
Infection Numbers: 64 – 36 = 28 averted

Quarraisha & Salim S Abdool Karim – IAS AIDS 2010 Vienna
PrEP Program Musts

- Safety screening
- Behavioral support
- Medical Care
- Community level monitoring
What about a “Cure”?  

- Sterilizing cure  
- Functional “cure”  

*Anti-virals alone don’t cure*  

- Eradication (Reservoirs?)  
- Immune system strengthening  
- Inflammation?  
- Host susceptibility
Current Issues – “Cure”

- No current therapeutic vaccine trials
- IL-2 proven ineffective
- Challenges with study design
- Berlin patient apparently cured but...
Long-Term Control of HIV by CCR5 Delta32/Delta32 Stem-Cell Transplantation


“Berlin patient”

CCR5Δ32 donor

CROI 2011 #147 Paula Cannon, et al
CCR5 Knock-out in Hematopoietic Stem Cells
Long-Term Control of HIV by CCR5 Delta32/Delta32 Stem-Cell Transplantation

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mosner, B.S., Susanne Gampf, M.D., Arne Müßig, M.D., Kristina Allen, Ph.D., Thomas Schneider, M.D., PhD, Jörg Hofmann, Ph.D., Claudia Kücherer, M.C., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.

CCR5 Knock-out in Hematopoietic Stem Cells
Zinc finger nucleases

Zinc fingers bind DNA, specificity conferred by apical residues

ZFN - DNA targeting zinc finger array, fused to nuclease domain

CGCTAATTGCACATGCTGATCCGAGA
GCGATTAACGAGTACGTACCCTAGGCTCA

CROI 2011 #147 Paula Cannon, et al
CCR5 Knock-out in Hematopoietic Stem Cells
Genome Editing of CCR5: Overview of Phase I Approach

Blood donation → Enrich CD4+ → Activate and expand by anti-CD3/CD28 coated beads (9-11 days) → Cryopreserve cell product SB-728-T → Infuse

Endpoints: Safety, CD4/HIV levels, CCR5 selection

Human Gene Transfer Protocol #0704-843
NIH/OBA/RAC approval June 20, 2007; FDA Approval Feb 2009

Clinicaltrials.gov NCT00842634 and NCT01044654

CROI 2011 #165 Carl June et al, Disruption of CCR5 in Zinc Finger Nuclease-treated CD4 T Cells: Phase 1 Trials
SB-728-T Increases CD4 T-Cell Counts from Baseline in all Subjects

CROI 2011 #165 Carl June et al, Disruption of CCR5 in Zinc Finger Nuclease-treated CD4 T Cells: Phase 1 Trials
Persistence of SB-728-T in the Peripheral Blood in all Subjects

The pentamer assay captures ~25% of all CCR5 disruptions:

$\Rightarrow$ total CCR5 gene disruption is ~ 4 fold higher

CROI 2011 #165 Carl June et al, Disruption of CCR5 in Zinc Finger Nuclease-treated CD4 T Cells: Phase 1 Trials
CROI 2011 #147 Paula Cannon, et al
CCR5 Knock-out in Hematopoietic Stem Cells
What’s Next?

- Vaccines – Understanding immunity and synergies, electroporation
- Microbicides – vaginal *
- Microbicides - rectal
- PrEP – oral and topical
  - dosing, new agents, rings, LT delivery
- “Cure”
  - reservoir clearance, IL-7, inflammation
Our Voice Must Be Heard

- Priorities (including CURE!)
- Study design
- Safety vs. risk
- Culturally relevant interventions
- Commitment (long term access)
- Implementation & Marketing
General Advocacy Goals

• Early, formal, real inclusion of consumers in processes:
  - Grant making
  - Prioritization
  - Protocol design
  - Communications
• Transparency
• Funding, Funding, Funding!
THANKS!
Butch McKay, Positively Living, & OASIS
Victoria Harris, EdD and the
TN AIDS Education and Training Center
Conference on Retroviruses and
Opportunistic Infections Scientific
Program Committee and Community
Liaison Subcommittee
AVAC, IRMA, PJA
YOU!
Contact info:

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615-715-1517
Advocacy Successes

- Expanded access
- Prioritization of issues:
  - Hepatitis C
  - Accelerated aging
- Prioritization of enrollment diversity:
  - Gender
  - Race / Ethnicity
  - Age
- NIH favors studies that address access
- Publication / information access