DARDAR Study

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Specific Aims

1. To define risk factors for HIV-associated disseminated TB (dTB)

2. To assess the safety and efficacy of a prime-boost immunization strategy using inactivated *Mycobacterium vaccae* (MV) for the prevention of HIV-associated pulmonary and disseminated tuberculosis

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Vaccine development goal

When we first started our vaccine studies the goal was - -

Timely development of an immunization strategy for the prevention of HIV-associated tuberculosis

Vaccine development goal

Timely development of an immunization strategy for the prevention of HIV-associated tuberculosis

Therefore:

- Existing investigational product
- Safe in HIV (i.e., not live)
- Multiple mycobacterial antigens

Inactivated vaccines

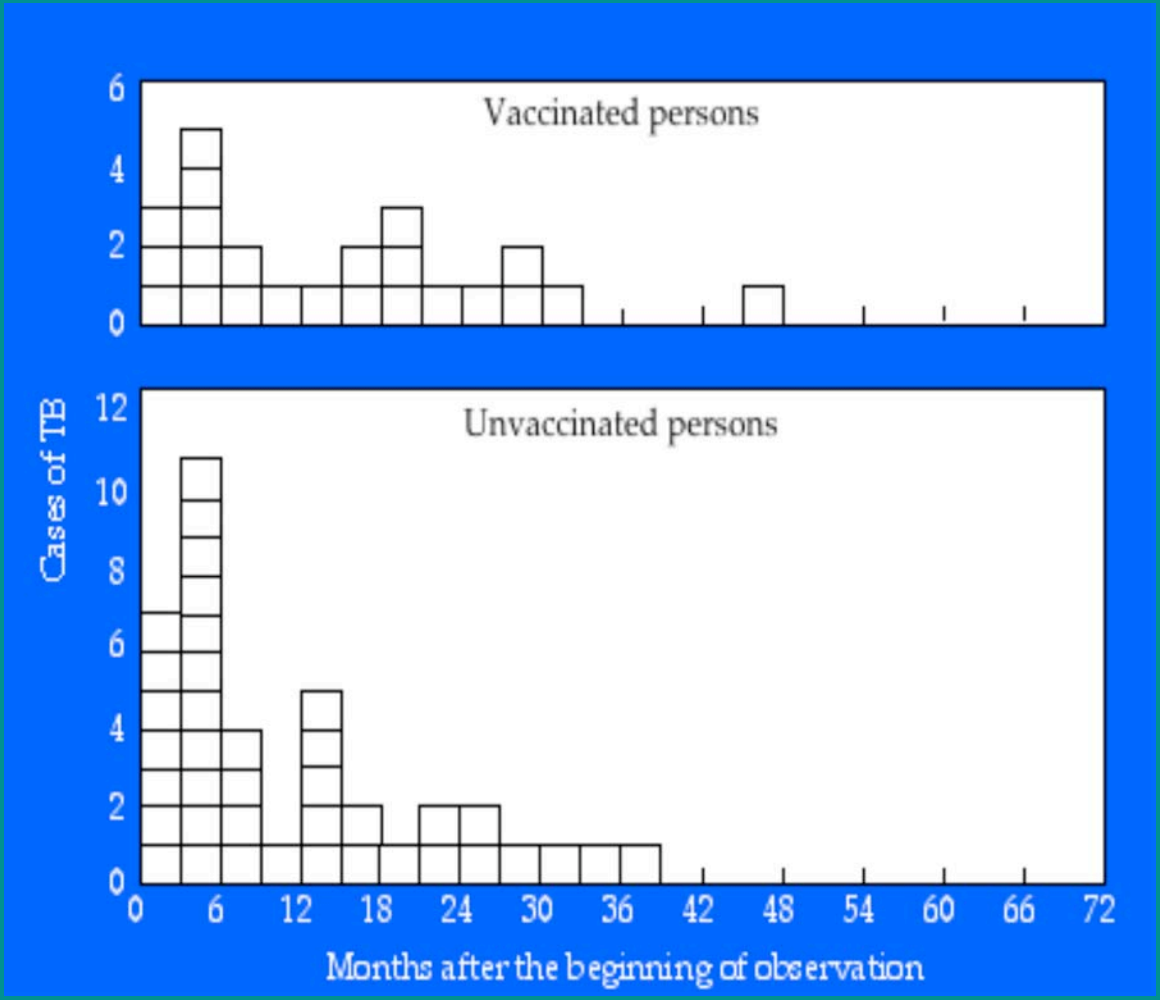
Viral : inactivated polio, hepatitis, influenza

Bacterial: typhoid, cholera, plague, TB

Potential limitations:

- Multiple doses required
- Local reactogenicity
- Durability

Prevention of TB by 5 doses of inactivated *M. bovis*



TB disease rates
vaccine: 11% (23/210)
control: 19% (39/206)
efficacy = 42%

Opie et al. 1939 conducted in a psychiatric hospital in Jamaica

-Opie, 1939

Immunologic protection against TB in humans

Natural infection

- Prior infection/disease with MTB
- Prior infection with non-tuberculous mycobacteria (NTM)

Vaccines

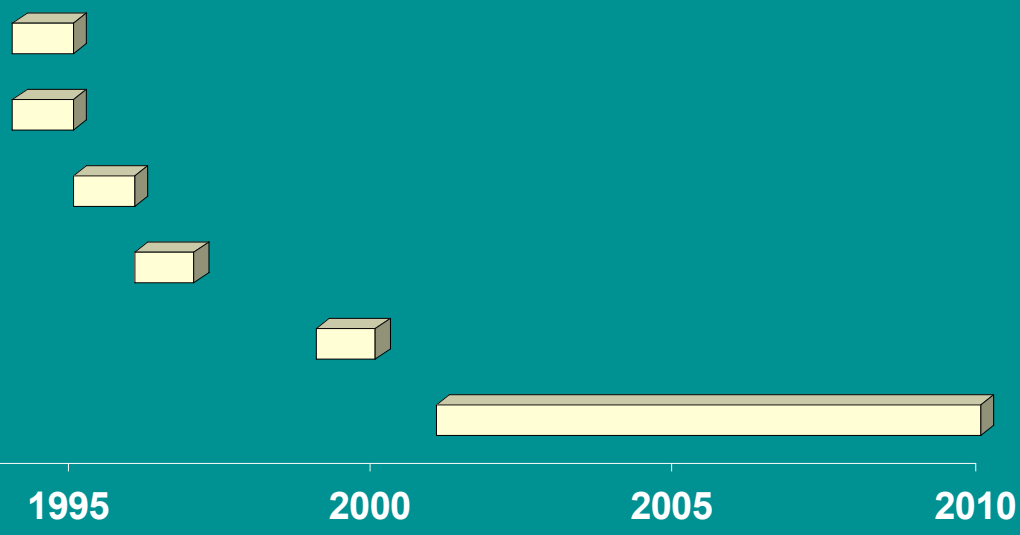
- Live *M. bovis* BCG
- Live *M. microti* (vole bacillus)
- Inactivated whole cell mycobacterial vaccines:
  - -*M. bovis* (Jamaica)
  - -combination of MAC/MB/MTB (Italy)

Inactivated NTM vaccine: *M. vaccae*

- Investigational heat-killed preparation produced by UK Health Protection Agency CAMR, for SR Pharma
- Demonstrated safety in humans
- Mouse studies indicate immunogenicity and efficacy in preventing MTB infection
  - **protects against aerosol TB [Hernandez-Pando]**
  - **induces CD8+ cells specific for TB [Skinner]**
  - **reduces mortality from IV TB [Abou-Zeid]**
  - **2 doses provide protection = BCG [Tan, unpublished]**
- Clinical studies by other investigators (single dose)

MV Phase I, II and III Trials

Phase	Site	MV (N)	Control (N)
1	US	9	0
	US	23	12
	US	11	0
2	Zambia	22	22
	Finland	19	20
3	Tanzania	~1000	~1000

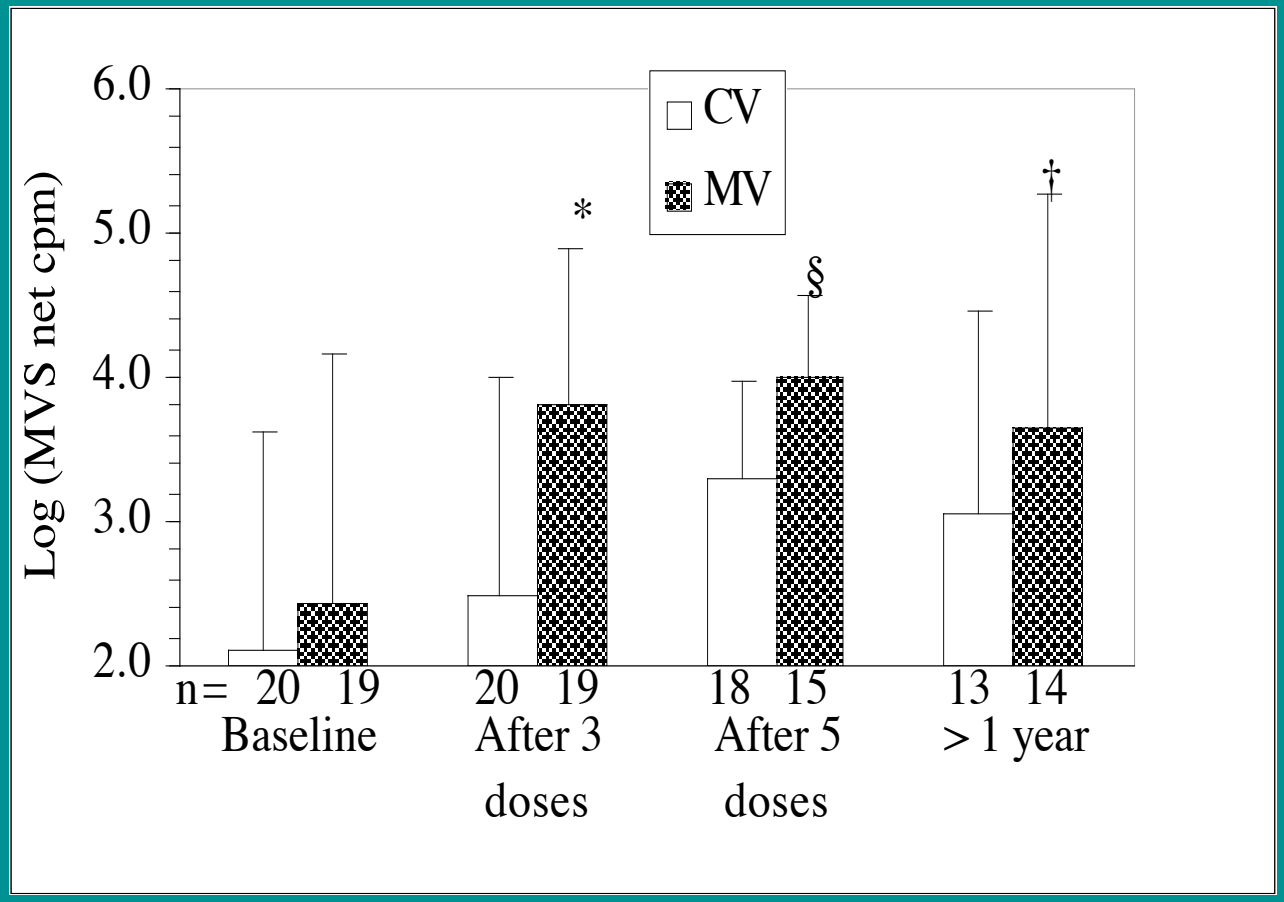


Finland: LPA to *M. vaccae* sonicate

Study population:
HIV pos, BCG pos

CV = control vaccine
MV = MV vaccine

LPA = lymphocyte proliferation assay




DARDAR HEALTH PROJECT
MUHIMBILI UNIVERSITY COLLEGE OF HEALTH SCIENCES
AND
DARTMOUTH MEDICAL SCHOOL
1797

DARDAR Study (Dartmouth/Dar es Salaam, Tanzania)
Double blind, RCT of a prime-boost strategy to prevent TB in persons with HIV infection

2000 HIV-positive persons
CD4>200
BCG scar

→ Randomize 1:1

→ 1000 placebo x5 (0,2,4,6,12 mos)

→ 1000 *M. vaccae* x5 (0,2,4,6,12 mos)

Hypothesis: 50% reduction in disseminated TB

Endpoints: 1°-disseminated TB (blood), 2°-pulmonary TB

Study duration: 2001-2009

All subjects are followed every 3 months for routine care of HIV and for detection and treatment of new cases of tuberculosis

All subjects have LPAs and IFNγ assays to mycobacterial Ags at baseline and after 5 doses of vaccine.


CLINIC ROOM


GRIP

DARDAR: Current status

Screened	4,973
Randomized	2,013
Lost to follow-up >6 mo.	241 (12%)
Deaths	172 (9%)
Doses of vaccine given	9,468
Disseminated TB endpoints	19
Pulmonary/other TB endpoints	121

Study completion expected in early 2009

DARDAR: Findings to date

- 12% of screened subjects have active TB at baseline
- 10% of active TB cases at baseline are “subclinical” or incipient (Clin Infect Dis 2005)
- All enrolled subjects have detectable immune responses to mycobacteria (J Infect Dis 2007)
- Pulmonary TB endpoints: 33% culture confirmed, 40% based on Sx, CXR, response to Rx (Vienna, 2006)
- Disseminated TB endpoints: terminal complication, false neg automated blood cultures (Capetown Nov 2007)

DARDAR: Previously undiagnosed TB at baseline

- Screening protocol

  Sx, CXR, sputum AFB (and culture if CD4>200)
- 258 (14%) of first 1794 required Rx for active TB

  CD4<200: TB Rx in 121 (20%) of 617

  CD4>200: TB Rx in 136 (12%) of 1136
- Basis for treatment in 136

  CXR alone: 68 (50%)

  CXR and Sx: 44 (32%)

  Sp culture: 13 (10%)

  Sx only: 11 (8%)

-Bakari, Arbeit, von Reyn et al, 2007

HIV/AIDS MAJOR ARTICLE

High Rates of Clinical and Subclinical Tuberculosis among HIV-Infected Ambulatory Subjects in Tanzania

10% of active TB cases at baseline are "subclinical" or incipient with no symptoms, negative CXR and typically negative AFB smears…

-Mtei et al Clin Infect Dis 2005

MAJOR ARTICLE

Baseline Mycobacterial Immune Responses in HIV-Infected Adults Primed with bacille Calmette-Guérin during Childhood and Entering a Tuberculosis Booster Vaccine Trial

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Background. Most new tuberculosis vaccines will be administered as a booster to subjects primed with bacille Calmette-Guérin (BCG) during childhood.

Methods. We investigated in vivo and in vitro immune responses to mycobacteria in human immunodeficiency virus (HIV)–positive subjects in Tanzania primed with BCG during childhood and entering a tuberculosis booster vaccine trial. Tests included intradermal skin testing for *Mycobacterium tuberculosis* purified protein derivative (PPD) and *Mycobacterium avium* sensitin (MAS); lymphocyte proliferation assays and interferon (IFN)–γ levels after stimulation with *Mycobacterium vaccae* sonicate (MVS), *M. tuberculosis* early secreted antigen (ESAT)–6, *M. tuberculosis* antigen 85 (Ag85), or *M. tuberculosis* whole-cell lysate (WCL); and determination of serum antibody to lipoarabinomannin (LAM).

Results. A total of 888 subjects with CD4 cell counts ≥200 cells/mm^3 were enrolled. PPD and MAS test results were positive in 34% and 30% of the subjects, respectively. Proliferative responses were detected as follows: MVS, 6%; Ag85, 24%; ESAT-6, 21%; and WCL, 59%. IFN-γ responses were 2%, 6%, 12%, and 38%, respectively. LAM antibody was detected in 28% of the subjects. Subjects were more likely to have detectable proliferative and IFN-γ responses if they had positive PPD test results or CD4 cell counts ≥500 cells/mm^3. Overall, 94% of the subjects had evidence of primed mycobacterial immune responses.

Conclusion. Of HIV-positive BCG-immunized adults with CD4 cell counts ≥200 cells/mm^3 in Tanzania, 94% are primed for booster mycobacterial immunization.

Evolving data suggest that the optimal immunological approach to an improved immunization strategy against tuberculosis is a prime-boost strategy: administration of a priming antigen followed by a heterologous boosting antigen [1–5]. Because most countries in which tuberculosis is endemic administer bacille Calmette-Guérin (BCG) at birth, many candidate tuberculosis vaccines will first be tested as booster vaccines in subjects who were primed with BCG at birth [6]. Persons with HIV infection are at the highest risk of morbidity and mortality from tuberculosis and represent a priority for the development of improved tuberculosis vaccine strategies [7]. Baseline cellular and humoral immune responses to mycobacteria after BCG vaccination have been characterized in HIV-negative individuals [8, 9] but not in a large cohort of HIV-infected adults with a history of childhood BCG immunization, to evaluate their suitability for boosting. Here, we present data on skin test results and in vivo responses to mycobacterial antigens among HIV-infected subjects entering a phase 3 tuberculosis booster vaccine trial in Tanzania (the DARDAR Study).

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Potential conflicts of interest: none reported.

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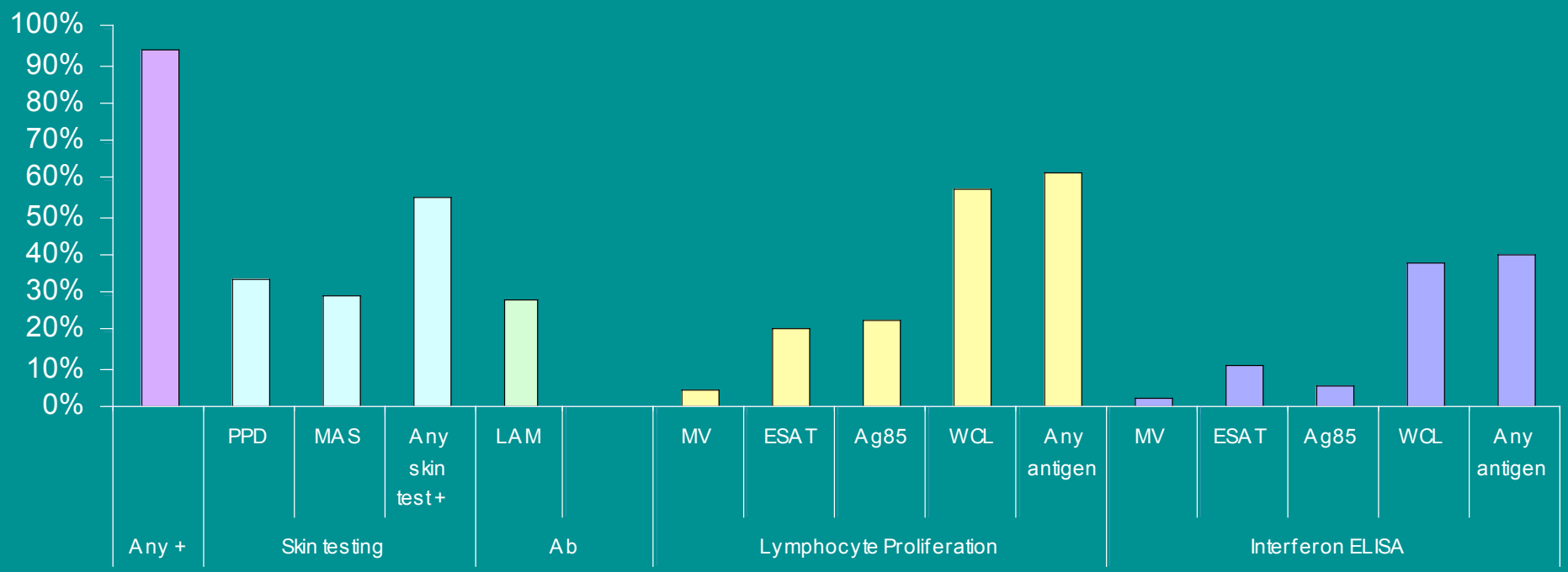
DARDAR: Baseline mycobacterial immunity



DARDAR 2 ° endpoint: pulmonary and extrapulmonary TB

Definite

- pos sterile site culture
- *or* 1 pos sputum culture with >10 cfu
- *or* 2 pos sputum smears or 2 cultures with 1-9 cfu

Probable

- 1 pos sputum smear or culture
  plus either pos CXR or pos Sx
- *or* Sx/signs plus CXR plus response to Rx

Possible

- Sx/signs plus CXR plus response to Rx

DARDAR: Case definitions

Suspect cases classified to date	**112**
Definite TB or Probable TB by study definition	**76 (68%)**
Positive culture for MTB (any site)	**36 (32%)**
TB bacteremia *(6 with blood as only pos microbiology)*	**12 (11%)**
Probable TB based on Sx, CXR, and response to Rx (*the largest single diagnostic category)*	**30 (28%)**

Disseminated TB cases (n=20)

Blood cultures

Blood culture method: automated MB/BacT (bioMerieux) incubated for 42 days, non-shaking

Early experience of positive cultures @ 40-41 days

Added routine subculture at 42 days to LJ medium

Time to positive: range 19-106 days

median 53 days

mean 52 days

Median survival of patients: 30 days

Message: High index of suspicion

DARDAR: Summary

- Phase III TB vaccine trial with GCP is near completion in Tanzania
- In a setting of endemic TB, HIV-positive subjects
  - have high rates of TB at baseline and
  - have high rates of TB endpoints on follow-up
- Among HIV-positive subjects with BCG scars, virtually all have demonstrable immune responses to mycobacterial antigens
- Blood cultures for disseminated TB typically positive only after death
- Pulmonary TB endpoints require case definitions

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Consent

- Six pages total (translated in Swahili)
- You may get vaccine or placebo
- We will give INH if TB skin test positive
- We will Dx and Rx TB and other infections
- Visits every 3 months, CD4 blood test each year
- Pregnancy tests
- Contact person (confidante, since stigma persists)
- Risks: Skin test or vaccine site reaction, allergy, reaction to INH
- Benefits: If vaccine effective all placebo recipients get vaccine at the end of the trial