# HIV Vaccine Research
# An Africa Perspective

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MTN Regional Meeting

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HIV VACCINE
TRIALS NETWORK

# HIV Vaccine Efficacy Trials/Concepts

| TRIAL | VACCINE | Antigen | Clade | Population | Vaccine Efficacy (VE) |
|---|---|---|---|---|---|
| Vax003 | AIDSVAX B/E | A244, MN, gD | B/E | Thai IDU | 0.1% (-31, 24%) |
| Vax004 | AIDSVAX B/B | MNE8, MN, gD | B/B | MSM | 6% (-17, 24%) |
| Step | MRK rAd5 | Gag, Pol, Nef | B | MSM | futility |
| Phambili | MRK rAd5 | Gag, Pol, Nef | B | S. African High incidence heterosexual | halted |
| RV144 | ALVAC-HIV + AIDSVAX B/E | 92TH023 gp120; LAI gag/pro, A244, MN gD | E/B | Thai low risk community | 31.2% (1, 52) |
| HVTN505 | DNA + rAd5 (VRC) | Gag (D/A), Pol (D/A), Nef (D), Env (D/A) | Gag B, Pol B, Nef B, Env (A, B, C) | MSM | enrolling |

# RV144 Trial Design → Results

**Sponsor:** US Army

**Partners:**
Thai MOH & Royal Thai Army
Division of AIDS, NIH
sanofi pasteur
GSID (VAXGEN)

**Prime:** ALVAC vCP1521
**Boost:** VAXGEN env protein boost
**Schedule:** 0,1,3,6 months
16,000 volunteers
1:1 vaccine:placebo
Follow-up for 3 years

Rayong & Chonburi Provinces, Thailand

Elicit combination of T-cell (prime) & antibody (boost) responses

Matched to circulating clades (B, E)
Test-of-concept, not for licensure

Protective Efficacy = 31.2%
3.5 years after first vaccination
P = 0.04 95% CI: 1.1 – 52.1%
No effect on viral load

| | mITT | |
|---|---|---|
| ***month*** | *Events* | *Efficacy* |
| **6** | 16 | 54% |
| **12** | 42 | 60% |
| **18** | 67 | 44% |
| **24** | 82 | 36% |
| **30** | 95 | 36% |

Vaccine Efficacy Highest @ 6-12 mos

- RV144 demonstrated partial (31%) efficacy with ALVAC/gp120 prime boost regimen
- In follow-up to these modest efficacy results, two simultaneous clinical strategies are needed:
  - An experimental (Research) focus with concurrent active arms using an adaptive study design
    - planning for iterative development
    - This strategy will provide data on vectors and regimens other than those to be used in the clinical development path
  - A clinical development (Licensure) focus using standard study designs
    - planning for success
    - the shortest possible path to licensure will be pursued to develop a pox/protein prime-boost vaccine with potential efficacy in populations at risk in Africa and Thailand
  - Data supporting correlates and licensure may be obtained with both strategies.

# Mutually supportive Phase IIb trials in South Africa and Thailand

- common immunization regimen using poxvirus vector prime/rgp120 protein boost (primary series and booster dose) to:
  - Confirm vaccine efficacy in key populations, including high-risk heterosexual populations in South Africa and high-risk MSM groups in Thailand;
  - Extend testing to populations where non-clade E viruses circulate;
  - Advance the pox-protein concept in populations where HIV prevalence is highest.
  - Allow earliest possible licensure of HIV vaccine.

Successful studies in Thailand and South Africa will address the epidemic in key target populations with different HIV subtypes. These mutually supportive studies are critical components of the P5 strategy.

# Pox-Protein Development Plan

Research

## Ongoing RV144 Follow-up in Thailand

***Studies:***
RV144i immune correlates studies
RV305 protein boosting study
RV306 expanded immunogenicity study
***Objective:***
Determine correlate of protection for use in future trials; optimize the regimen
***Partners/Funders:***
US Army, Thai Gov't, NIH, sanofi pasteur, BMGF

## S. Africa ph2b

***Population:*** Heterosexual, high-risk
***Products:*** DNA + NYVAC (sanofi) + gp140 (Polymun)/MF59 (NVD)
vs. NYVAC (sanofi) + gp140 (Polymun)/MF59 (NVD)

***Objective:*** Extend results & accelerate evaluation of other products using adaptive trial design and first available protein

***Partners/Funders:*** NIH, HVTN, sanofi pasteur, Novartis, BMGF

Licensure

## Thailand

***Population:*** MSM, high-risk
***Products:*** ALVAC (sanofi) + gp120/MF59 (NVD)

***Objective:*** Confirm result & demonstrate efficacy in target population with potential for licensure

***Partners/Funders:*** US Army, Thai Gov't, NIH, sanofi, BMGF?

## S. Africa

***Population:*** Heterosexual, high-risk
***Products:*** ALVAC (sanofi) + gp120/MF59 (NVD)

***Objective:*** Extend result & translate vaccine to Africa, other high-risk groups

***Partners/Funders:*** NIH, HVTN, sanofi, Novartis, BMGF, RSA?

**Candidate selection**

- ALVAC is default vector prime
- Proteins boosts TBD
- RV144 immune correlates
- Immune grid
- Cost, product availability



| 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 |
|---|---|---|---|---|---|---|---|

# Strategy Objective: To Increase Vaccine Efficacy from 30% to ≥ 50%

- Scientific rationale & feasibility
  - Vaccine efficacy (VE) at 12 mos was 60% in RV144
  - Boosting may impact protection level / durability
    - Vi-Cholera – Taylor et al., (1997) Journal of Infectious Disease, Vol. 181, pg 1667- 1673
    - Meningococcal Cj – Perret et al., (2010) Clin Infect Dis, Vol. 50, pg 1601-1610
  - Alternative adjuvant may impact magnitude, quality and durability of the response

- VE 50% for 3 years would offer a significant public health benefit for regional epidemics in Thailand and South Africa

# Licensure Trial Example Schema

- 1 vaccine regimen vs. placebo

| Hypothetical Schema of a Vaccine vs. Placebo Trial | | | | | | |
|---|---|---|---|---|---|---|
| Study Arm | Number Subjects | Month 0 | Month 1 | Month 3 | Month 6 | Month 12 |
| Vaccine | 2500 | ALVAC | ALVAC | ALVAC + prot | ALVAC + prot | ALAC + prot |
| Placebo | 2500 | Placebo | Placebo | Placebo | Placebo | Placebo |
| Total | 5000 | | | | | |

- HIV negative subjects enrolled and tested for HIV infection 3-monthly for a maximum of 36 months

# Objectives of the Licensure Trial

- Primary objective:
  - Evaluate VE against infections diagnosed within 24 months of randomization [i.e., VE(0-24)]
- Secondary objectives:
  1. To evaluate durability of VE out to 36 months if there is reliable evidence for positive VE(0-24)
  2. To evaluate immune correlates of protection if the vaccine regimen shows reliable evidence for positive VE(0-24), including sieve analysis
  3. To evaluate vaccine effects on HIV-1 progression for 18 months post-diagnosis, including viral load, CD4+ T cell count, HAART, and AIDS endpoints
- Exploratory objectives:
  - Several, including behavioral assessments with emphasis on PrEP use

# Research Trial Example Schema

- 2 vaccine regimens vs. a shared placebo group

| Hypothetical Schema of a 2-Vaccine Arm vs. Placebo Trial | | | | | | | |
|---|---|---|---|---|---|---|---|
| Study Arm | Number Subjects | Month 0 | Month 0.5* | Month 1 | Month 3 | Month 6 | Month 12 |
| Vaccine 1 | 2150 | NYVAC | Placebo | NYVAC | NYVAC + prot | NYVAC + prot | NYVAC + prot |
| Vaccine 2 | 2150 | DNA | DNA | DNA | NYVAC + prot | NYVAC + prot | NYVAC + prot |
| Placebo | 2150 | Placebo | Placebo | Placebo | Placebo | Placebo | Placebo |
| Total | 6450 | | | | | | |

*Depending on HVTN 092 results, the schema may not include the Month 0.5 injections

- HIV negative subjects enrolled and tested for HIV infection 2-monthly for a maximum of 36 months

# Objectives of the Research Design

- Primary objective:
  - For each vaccine regimen, evaluate VE against infections diagnosed within 18 months of randomization [i.e., VE(0-18)]

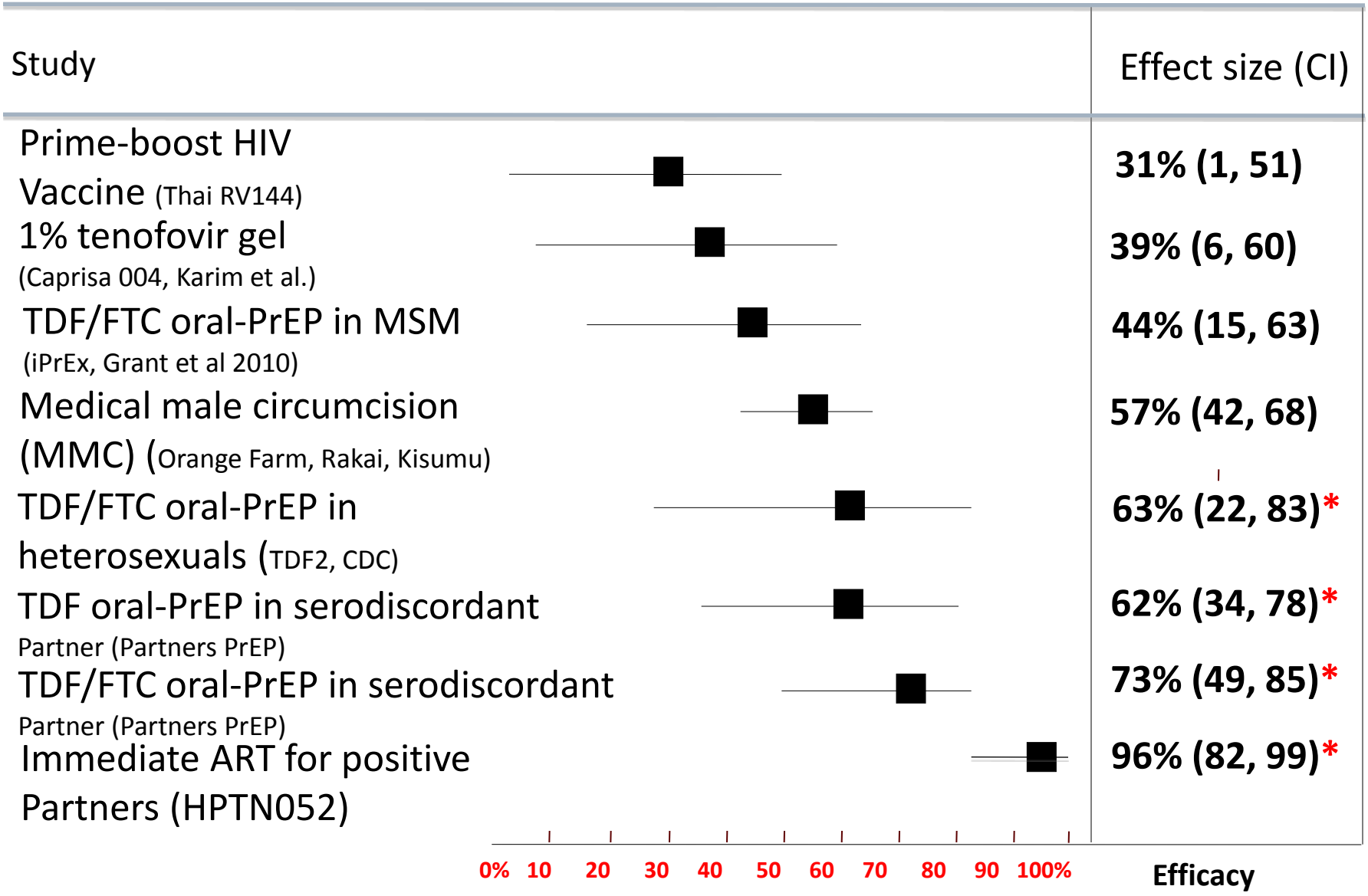
- Secondary objectives:
  1. To evaluate durability of VE out to 36 months for each regimen showing reliable evidence for positive VE(0-18)
  2. To expeditiously and rigorously evaluate immune correlates of protection if any of the vaccine regimens show reliable evidence for positive VE(0-18), including sieve analysis
  3. To compare VE between the 2 vaccine regimens
  4. To evaluate vaccine effects on HIV-1 progression for 18 months post-diagnosis, including viral load, CD4+ T cell count, HAART, and AIDS endpoints

- Exploratory objectives:
  - Several, including behavioral assessments with emphasis on PrEP use

# Design features

- Measure VE two time points (early VE and durability)
- Protein Boost for durability
- Clade Specific
- Endpoints
- Prep/Microbicide/MMC
- Regulatory issues to consider when using combination prevention
- Cost

# New biomedical intervention strategies




*Provisional

## What are key study design considerations as we move towards future combination interventions

- Appropriate choice of study populations
  - E.g. implications of HPTN 052
- Appropriate choice of control groups
  - What is the standard of care prevention package
- What is the sample size: science vs. efficiency
  - Impact of partially effective interventions on baseline incidence
- Defining outcomes and endpoints of interest
  - How to define and evaluate endpoints: immune correlates of protection, viral load, HIV infection
  - How to evaluate and monitor impact on change in incidence, prevalence, mortality, other outcomes of interest

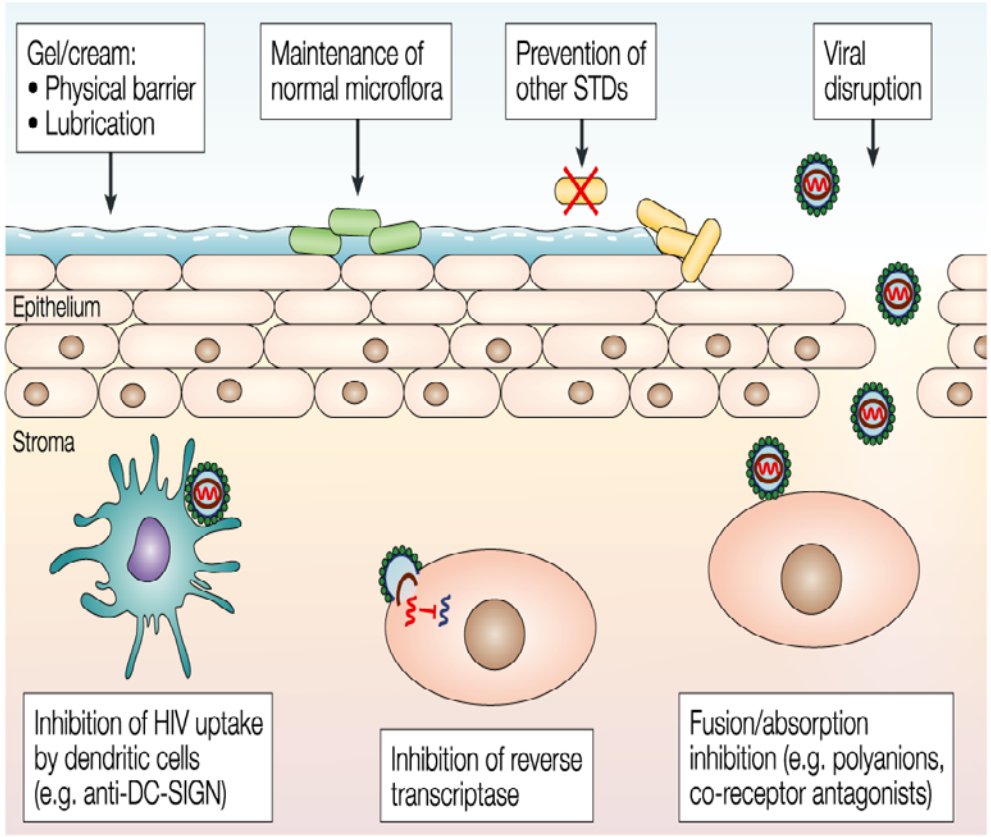
# How might (VAX and PrEP) deliver better protection?

- Providing protection during the immunization period
- Reducing infectious challenge and primary foci of infection
- Increase eclipse phase prior to systemic dissemination providing an extended opportunity for adaptive immunity to respond
- Boosting local immunity (virus/antigen)
- Broadening localized immunity through protected exposure to prevalent virus.
- Converting high risk challenge to low risk challenge (RV144)
- Coverage between potential re-vaccination campaigns as immunity wanes
- Providing immunological coverage of intermittent PrEP adherence, break through virus and resistance evolution

# How do new HIV interventions impact on the design of future HIV Vaccine Trials?

May complicate endpoint measurement

**ARV protection**




? Lower viral load set point

? Delay identification of acute infection

? Resistance

? Impact on natural history of HIV infection

? Impacts on genetic bottleneck

?impacts on immune markers or correlates

# HIV incidence and sample size

Higher prevention standard will impact on HIV incidence (Increase sample size)

| Annual incidence placebo arm | Test: VE=52% vs. VE<=20% VE(0-24) | Test: VE=58% vs. VE<=30% VE(0-24) |
|---|---|---|
| 2.0% | 3450 | 3650 |
| 2.5% | 2825 | 2950 |
| 3.0% | 2350 | 2450 |
| 3.5% | 2025 | 2125 |
| 4.0% | 1800 | 1850 |
| 4.5% | 1600 | 1675 |
| 5.0% | 1450 | 1500 |
| 5.5% | 1300 | 1350 |
| 6.0% | 1200 | 1250 |

Courtesy: Peter Gilbert & Jim Kublin

# Inter-Network Collaborations

- Inter-Network collaborations make sense as scientific agendae overlap and resources are limited
  - Draw on expertise of investigators from allied fields
- Progress in “drugs for prevention” arena has been substantial and relevance will only grow from this point on
- Multimodality approach to biomedical prevention needs to be incorporated into clinical trials
- PrEP – systemic and topical – is going to be an increasing reality for vaccine trials
  - There are scientific questions to answer before (or as) this becomes widespread

# HVTN – MTN Collaboration Genesis I

- Arose out of interest in vaccine + PrEP concept
  - Topic considered for a number of years
  - Recently intensively discussed in reference to HVTN 505 expansion and release of iPrEx results
  - With HVTN plans in South Africa, 1% TDF vaginal gel may become a standard of care for women at risk

# HVTN – MTN Collaboration Genesis II

- There has been an assumption that vaccines and PrEP (topical or systemic) may not interact but this question has not been prospectively answered and may not be true

  - e.g., nRTI's work intracellularly in target cells that may be affected by immunization

  - Topical and systemic PrEP may have different effects on mucosal immune responses given differences in local tissue concentrations and other factors

  - Effects could be synergistic, additive, neutral or antagonistic

# HVTN – MTN Concept

A Phase 1 Clinical Trial to Evaluate the Safety and Immunogenicity of DNA-C/NYVAC-C Prime Boost Vaccination With or Without Tenofovir/Emtricitabine or Tenofovir 1% Gel Administered Vaginally in Healthy, HIV-1 Uninfected Adult Female Participants

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# HVTN – MTN Concept: Primary Objectives

- To evaluate the safety and tolerability of DNA-C prime followed by NYVAC boost with and without oral FTC/TDF or topical TDF 1% gel in HIV-uninfected healthy adults

- To evaluate the systemic immunogenicity of the DNA-NYVAC vaccine regimen with or without systemic or topical PrEP

# HVTN – MTN Concept: Secondary Objectives

- To evaluate the mucosal immunogenicity of the DNA-NYVAC vaccine regimen with or without systemic or topical PrEP

- To evaluate the innate immune responses elicited by the DNA-NYVAC vaccine regimen with or without systemic or topical PrEP

# HVTN – MTN Concept Schema

| Study arm | Number | Study products[a] | Month -1 (Day -28 on)[b] | Month 0 (Day 0) | Month 1 (Day 28) | Month 2 (Day 56) | Month 5 (Day 140) |
|---|---|---|---|---|---|---|---|
| Group 1a (Vaccine + Oral PrEP) | 40 | **Vaccine**<br>**Oral FTC/TDF** | **Daily** | **DNA-C**<br>**Daily** | **DNA-C** | **DNA-C** | **NYVAC-C** |

y

immunogenicity timepoint at 2 weeks after the final study injection.

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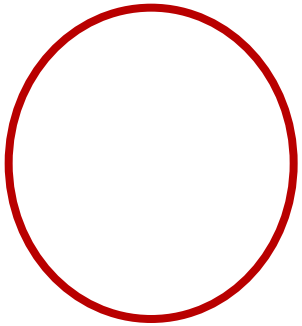

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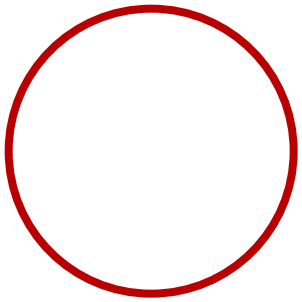

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immunogenicity timepoint at 2 weeks after the final study injection.

# How do new HIV interventions impact on the design of future HIV Vaccine Trials?

- Interventions like Tenofovir gel may not be licensed or available in country
- Procurement of intervention and who pays for the intervention?
- If submitted for licensure, company may not wish intervention to be used with another experimental intervention

# HVTN – MTN Collaboration Working Group

- Sharon Hillier
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- Magdalena Sobieszczyk
- Scott Hammer
- Shelly Karuna
- Carter Bentley
- Paul Edlefsen
- Jim Kublin
- Glenda Gray
- Jin Bae
- John Hural
- Jan Johannessen
- Laissa Ouedraogo
- Elizabeth Adams