HIVACAT
Projecte de Recerca de la Vacuna de la Sida

Generalitat de Catalunya
Departament de Salut

Generalitat de Catalunya
Departament d'Innovació, Universitats i Empresa

Obra Social
Fundació "la Caixa"

FUNDACIÓ CLÍNIC
BARCELONA

IrsiCaixa
Institut de Recerca de la Sida

IDIBAPS
Institut D'Investigacions Biomèdiques August Pi i Sunyer
1. General considerations

2. Therapeutic vaccines against HIV. Dendritic cells

3. Preventive vaccines against HIV. Other strategies for prevention

4. Final considerations
Preventive vaccine

Per year:
> 600 Catalunya
> 3000 Spain
> 3 M World

30 M +
(85% in developing countries)

ART for life
Eradication
Therapeutic vaccine (functional cure)
1. General considerations

2. Therapeutic vaccines against HIV. Dendritic cells
   - Functional cure

3. Preventive vaccines against HIV. Other strategies for prevention

4. Final considerations
THERAPEUTIC VACCINE AGAINST HERPES ZOSTER

Vaccines against rabies, tetanus and diphtheria are therapeutic

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**Figure 2. Kaplan–Meier Estimates of the Effect of Zoster Vaccine on the Cumulative Incidence of Postherpetic Neuralgia (Panel A) and Herpes Zoster (Panel B) in the Modified Intention-to-Treat Population.**

Incidence rates of postherpetic neuralgia (PHN) and herpes zoster (HZ) were significantly lower in the vaccine group than in the placebo group (P<0.001, by a stratified log-rank test that pooled the results of the log-rank test from the two age groups). Cumulative incidence, expressed as a percentage of the subjects at risk, is the probability of the development of the disease during the period from 30 days after vaccination to the follow-up time.
The immune system is not able to “contain” VL rebound even after a long term successful suppressive ART.

Conversely, the aim of an immunogen or a therapeutic vaccine should be to avoid VL rebound after interruption of ART.
Therapeutic vaccines against HIV infection

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Modalities of therapeutic vaccines tested in clinical trials

- Whole inactivated virus: 1
- Subunit vaccines: 4
- Vaccines using DNA as vector: 4
- Viral vector vaccines: 12
- Dendritic cells based vaccines: 2
Timelines Therapeutic Vaccines

DCV2
- DCV2 2nd arm & trial data

DCV3
- DCV3 trial data

Development of pNL4.3/ΔRT/ΔGag chimeras
- In vitro production & characterization of NL4.3/ΔRT virions & chimeras
  NL4.3/ΔRT/ΔGag, NL4.3/ΔRT/ΔNef, NL4.3/ΔRT/ΔEnv
- Development of safe recombinant chimeras Nef & Env and double chimeras
- Characterization, immunogenicity studies & analysis

Δ-RT/Δ-Int +/- chimeras

MVA/chimp-adoeno
- Phase I clinical trial & data analysis

RISVAC03 - MVA
- Phase I clinical trial & trial data
- Phase II clinical trial

HIVACAT Current Period
- 2011
- 2012

HIVACAT Second Period
- 2013
- 2014
- 2015
- 2016
Therapeutic Immunization with Dendritic Cells Loaded with Heat-Inactivated Autologous HIV-1 in Patients with Chronic HIV-1 Infection

Felipe García,¹ Merylene Lejeune,² Nuria Climent,² Cristina Gil,³ José Alcamí,⁸ Vanessa Morente,⁴ Llucia Alós,⁴ Alba Ruiz,⁵ Javier Setoain,⁵ Emilio Fumero,¹ Pedro Castro,¹ Anna López,² Anna Cruceta,¹ Carlos Piera,⁵ Eric Florence,¹ Arturo Pereira,⁶ Agnes Libois,¹ Nuria González,⁸ Meritxell Guilá,³ Miguel Caballero,⁷ Francisco Lomeña,⁵ Joan Joseph,¹ José M Miró,¹ Tomás Pumarola,³ Montserrat Plana,² José M Gatell,¹ and Teresa Gallart²

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0022-1899/2005/19110-0014$15.00
HAART PLUS THERAPEUTIC VACCINE WITH AUTOLOGOUS MONOCYTE-DERIVED DENDRITIC CELLS (DC) LOADED WITH INACTIVATED AUTOLOGOUS HIV-1

CD4 > 500 cells/μL, PVL > 5000 copies/ml

**HAART**

- PVL < 20
  - w246

**STOP-1**

- w90
  - w78

**CASES N=12**

- PLASMAPHERESIS

**HAART**

- s.c. DC injections
  - Non-Pulsed DC
    - w0
      - 6w
        - 12w
          - 18w
            - 24w
              - d8

- Pulsed DC (4x10^6 virions/vaccine)

**STOP-2**

- w30

**HAART**

- Blood sample (60-80 ml) for DC generation

**CONTROLS N=6***

- PVL < 20

**HAART**

- *2 lost for follow-up
DCV-1 study

**Figure 3A**
Cases: $n=12$

**Figure 3B**
Patient #262

**Figure 3C**

**Figure 3D**
Controls: $n=4$
Inclusion criteria:
1. <20 copies/ml
2. Nadir >350 CD4+ T cells/mm³

**DCV2-b study**

**STOP 1**
- Virus culture
- Doses of pulsed MD-DC

**STOP 2**
- Blood sample (120 ml) for DC generation

**ARM III (N=12)**
- Doses of pulsed MD-DC

**ARM IV (N=12)**
- Doses of NON-pulsed MD-DC

**ARM V**
- CONTROL GROUP (N=12)

**HAART**
- Stop HAART
DCV-2b study (submitted)
Figure 5. Pre-ART vs. Week 12 of STI Log Change in Viral Load

Routy et al.
plasma viral load

months

HAART

TV

STOP HAART

5000000

5000000

500000

50000

5000

500

50

5
VACCINES AGAINST HIV-AIDS: 2011

1. General considerations

2. Therapeutic vaccines against HIV. Dendritic cells
   - Discordant CD4 response
   - Eradication (ERAMUNE study)
   - Reduce reservoirs (ERAMUNE study)
   - Minimize inflammation / immune activation
   - Minimize needs of ART

3. Preventive vaccines against HIV. Other strategies for prevention

4. Final considerations
Inclusion criteria
1. > 10000 c/ml
2. Nadir >350 CD4+ T c/mm³

-6 0 2 4

ARM I (N=12)
ARM II CONTROLS (N=12)

48 WEEKS

Garcia F et al. JID, 2011
VIRAL LOAD RESPONSES

IT WAS OBSERVED A MODEST DECREASE OF VL IN VACCINATED PATIENTS
plasma viral load

Therapeutic vaccine

Less ART?
Later ART?
Preventive vaccine

Per year:

> 600 Catalunya
> 3000 Spain
> 3 M World

ART for life
Eradication
Therapeutic vaccine (functional cure)

7000 M

30 M +
(85% in developing countries)
VACCINES AGAINST HIV-AIDS: 2011

1. General considerations

2. Therapeutic vaccines against HIV. Dendritic cells

3. Preventive vaccines against HIV. Other strategies for prevention

4. Final considerations
Efficacy of HIV Prevention Strategies From Randomized Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect Size, % (95% CI)</th>
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<tbody>
<tr>
<td>ART for prevention; HPTN 052, Africa, Asia, Americas</td>
<td>96 (73-99)</td>
</tr>
<tr>
<td>PrEP for discordant couples; Partners PrEP, Uganda, Kenya</td>
<td>73 (49-85)</td>
</tr>
<tr>
<td>PrEP for heterosexual men and women; TDF2, Botswana</td>
<td>63 (21-84)</td>
</tr>
<tr>
<td>Medical male circumcision; Orange Farm, Rakai, Kisumu</td>
<td>54 (38-66)</td>
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<tr>
<td>PrEP for MSMs; iPrEX, Americas, Thailand, South Africa</td>
<td>44 (15-63)</td>
</tr>
<tr>
<td>Sexually transmitted diseases treatment; Mwanza, Tanzania</td>
<td>42 (21-58)</td>
</tr>
<tr>
<td>Microbicide; CAPRISA004, South Africa</td>
<td>39 (6-60)</td>
</tr>
<tr>
<td>HIV vaccine; RV144, Thailand</td>
<td>31 (1-51)</td>
</tr>
</tbody>
</table>

Most efficient and cost effective intervention in the eradication (small pox, polio) or control of transmissible infectious diseases

Most are preventive
Some are “therapeutic”: rabies, difteria, tetanus, zoster
VACUNAS: COMPONENTE MAGICO

Efecto de la vacunación contra el sarampión

sarampión comunicado (miles)

introducción de la vacunación
Most effective vaccines have been discovered by trial and error without knowing the correlates of immune protection of natural disease or to prevent or modify the evolution of the disease.
Anticuerpos no neutralizantes
uso diagnóstico
control de la infección vacunas

Células citotóxicas (CD8, CTL’s)
uso diagnóstico
control de la infección rechazo de transplantes vacunas?
Immune system (innate, Ab, CMI, mucosal) is the natural tool to identify, protect, eradicate and/or modulate the evolution of transmissible infectious diseases

After a first contact is able to generate a quick memory response

Limited variability of offending pathogens. Cross reactivity

Remains intact during the course of most infections
Anticuerpos no neutralizantes

Anticuerpos neutralizantes

Células citotóxicas (CD8, CTL’s)

Uso diagnóstico

Control de la infección

Vacunas

Rechazo de transplantes

Vacunas?
<table>
<thead>
<tr>
<th>Virus</th>
<th>Type of vaccine</th>
<th>Vaccine-induced protective immunity</th>
<th>Mechanisms of immune control during virus infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>Live</td>
<td>Antibodies, CTL</td>
<td>CTL</td>
</tr>
<tr>
<td>Rabies</td>
<td>Killed virus</td>
<td>Antibodies</td>
<td>Antibodies, CD4, CTL</td>
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<tr>
<td>Polio</td>
<td>Live or killed virus</td>
<td>Antibodies</td>
<td>Antibodies</td>
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<td>Measles</td>
<td>Live</td>
<td>Antibodies; CTL</td>
<td>Antibodies, CD4, CTL</td>
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<tr>
<td>Mumps</td>
<td>Live</td>
<td>Antibodies</td>
<td>Antibodies</td>
</tr>
<tr>
<td>Rubella</td>
<td>Live</td>
<td>Antibodies</td>
<td>Antibodies</td>
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<tr>
<td>Varicella zoster</td>
<td>Live</td>
<td>Antibodies; CTL</td>
<td>Antibodies, CTL</td>
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<tr>
<td>Influenza</td>
<td>Protein</td>
<td>Antibodies</td>
<td>Antibodies, CD4, CTL</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Killed virus</td>
<td>Antibodies</td>
<td>Antibodies, CD4, CTL</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Protein</td>
<td>Antibodies</td>
<td>Antibodies, CD4, CTL</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>VLP</td>
<td>Antibodies</td>
<td>CD4, CTL</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>–</td>
<td>–</td>
<td>CD4, CTL</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>–</td>
<td>–</td>
<td>CD4, CTL</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>–</td>
<td>–</td>
<td>CD4, CTL</td>
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<tr>
<td>Herpes simplex virus</td>
<td>–</td>
<td>–</td>
<td>CTL</td>
</tr>
<tr>
<td>types 1 and 2</td>
<td>–</td>
<td>–</td>
<td></td>
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<tr>
<td>HIV-1 and HIV-2</td>
<td>–</td>
<td>–</td>
<td>CD4, CTL</td>
</tr>
<tr>
<td>Human herpesvirus 6</td>
<td>–</td>
<td>–</td>
<td>Antibodies, T cells</td>
</tr>
</tbody>
</table>
VACCINE AGAINST HIV-AIDS: 2011

Figure 1  Schematic representation of the effectiveness of the components of the antiviral immune response against different forms of HIV-1. Neutralizing antibodies are efficient in blocking virus particles but poorly effective against cell-associated virus, such as virus-infected cells. Some CTLs are effective against virus-infected cells but not against free virus particles. Neither antibodies nor CTLs are effective against latently infected cells.
Figure 1  Schematic representation of the effectiveness of the components of the antiviral immune response against different forms of HIV-1. Neutralizing antibodies are efficient in blocking virus particles but poorly effective against cell-associated virus, such as virus-infected cells. Some CTLs are effective against virus-infected cells but not against free virus particles. Neither antibodies nor CTLs are effective against latently infected cells.
VACCINE AGAINST HIV-AIDS: 2005

>= 20% variability
Diversidad

Global influenza 1996

HIV single Individual
6 years after Infection

HIV Amsterdam cohort 1991

Congo 1997

10%
Etapas tempranas de la infección por el VIH

- Captación y transporte del virus por células dendríticas.
- Infección CD4+ en la lámina propia y ganglios reginales.
- Diseminación masiva del VIH
  - Organos linfoides
  - Sistema nervioso central
  - Establecimiento de reservorios
  - Replicación persistente
  - Latencia

2 días

5 días

4-12 semanas

RESPUESTA INMUNE

Walker B. NEJM. 1998
Batalla de Normandia. Instalación de cabezas de puente
Costa de Normandía: playas de Utha, Ohama, Gold, Juno, Sword
VACCINE AGAINST HIV-AIDS: 2011

- Live attenuated vaccine
- Inactivated vaccine
- Recombinant vector

Diagram:
- Mucosal immunity
- Neutralizing
- T cell immunity
- Innate immunity

Questions:
- ??
- ?
Placebo-Controlled Phase 3 Trial of a Recombinant Glycoprotein 120 Vaccine to Prevent HIV-1 Infection

The rgp120 HIV Vaccine Study Group

(See the article by Gilbert et al., on pages 666-77, and the editorial commentary by Graham and Mascola, on pages 647-9.)

Background. A vaccine is needed to prevent human immunodeficiency virus type 1 (HIV-1) infection.

Methods. A double-blind, randomized trial of a recombinant HIV-1 envelope glycoprotein subunit (rgp120) vaccine was conducted among men who have sex with men and among women at high risk for heterosexual transmission of HIV-1. Volunteers received 7 injections of either vaccine or placebo (ratio, 2:1) over 30 months. The primary end point was HIV-1 seroconversion over 36 months.

Results. A total of 5403 volunteers (5095 men and 308 women) were evaluated. The vaccine did not prevent HIV-1 acquisition: infection rates were 6.7% in 3598 vaccinees and 7.0% in 1805 placebo recipients; vaccine efficacy (VE) was estimated as 6% (95% confidence interval, −17% to 24%). There were no significant differences in viral loads, rates of antiretroviral-therapy initiation, or the genetic characteristics of the infecting HIV-1 strains between treatment arms. Exploratory subgroup analyses showed nonsignificant trends toward efficacy in preventing infection in the highest risk (VE, 43%; n = 247) and nonwhite (VE, 47%; n = 914) volunteers (P = .10, adjusted for multiple subgroup comparisons).

Conclusions. There was no overall protective effect. The efficacy trends in subgroups may provide clues for the development of effective immunization approaches.
Viral envelope

α dominio interacción CD4

α dominio de fusión

(VBurton D. Human neutralizing antibodies and a vaccine for HIV-1. XIV International AIDS Conference [Abstract nº201])
vacuna

100%

Vacuna AIDSVax

100%
Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial

Susan P Buchbinder, Devan V Mehrotra, Ann Duer, Daniel W Fitzgerald, Robin Mogg, David Li, Peter B Gilbert, Javier R Lama, Michael Marmor, Carlos del Rio, M Juliana McElrath, Danilo R Casimiro, Keith M Gottesdiener, Jeffrey A Chodakewitz, Lawrence Corey, Michael N Robertson, and the Step Study Protocol Team*

Summary

Background Observational data and non-human primate challenge studies suggest that cell-mediated immune responses might provide control of HIV replication. The Step Study directly assessed the efficacy of a cell-mediated immunity vaccine to protect against HIV-1 infection or change in early plasma HIV-1 levels.

Methods We undertook a double-blind, phase II, test-of-concept study at 34 sites in North America, the Caribbean, South America, and Australia. We randomly assigned 3000 HIV-1-seronegative participants by computer-generated assignments to receive three injections of MRKAd5 HIV-1 gag/pol/nef vaccine (n=1494) or placebo (n=1506). Randomisation was prestratified by sex, adenovirus type 5 (Ad5) antibody titre at baseline, and study site. Primary objective was a reduction in HIV-1 acquisition rates (tested every 6 months) or a decrease in HIV-1 viral-load setpoint (early plasma HIV-1 RNA measured 3 months after HIV-1 diagnosis). Analyses were per protocol and modified intention to treat. The study was stopped early because it unexpectedly met the prespecified futility boundaries at the first interim analysis. This study is registered with ClinicalTrials.gov, number NCT00095576.

Findings In a prespecified interim analysis in participants with baseline Ad5 antibody titre 200 or less, 24 (3%) of 741 vaccine recipients became HIV-1 infected versus 21 (3%) of 762 placebo recipients (hazard ratio [HR] 1.2 [95% CI 0.6–2.2]). All but one infection occurred in men. The corresponding geometric mean plasma HIV-1 RNA was comparable in infected male vaccine and placebo recipients (4.61 vs 4.41 log₁₀ copies per mL, one tailed p value for potential benefit 0.66). The vaccine elicited interferon-γ ELISPOT responses in 75% (267) of the 25% random sample of all vaccine recipients (including both low and high Ad5 antibody titres) on whose specimens this testing was done (n=354). In exploratory analyses of all study volunteers, irrespective of baseline Ad5 antibody titre, the HR of HIV-1 infection between vaccine and placebo recipients was higher in Ad5 seropositive men (HR 2.3 [95% CI 1.2–4.3]) and uncircumcised men (3.8 [1.5–9.3]), but was not increased in Ad5 seronegative (1.0 [0.5–1.9]) or circumcised (1.0 [0.6–1.7]) men.

Interpretation This cell-mediated immunity vaccine did not prevent HIV-1 infection or reduce early viral level. Mechanisms for insufficient efficacy of the vaccine and the increased HIV-1 infection rates in subgroups of vaccine recipients are being explored.

Funding Merck Research Laboratories; the Division of AIDS, National Institute of Allergy and Infectious Diseases, in the US National Institutes of Health (NIH); and the NIH-sponsored HIV Vaccine Trials Network (HVTN).
Adenovirus
Step trial

- Double-blind phase IIB test-of-concept of the MRKAd5 HIV-1 subtype B gag/pol/nef vaccine.
- Immunizations were interrupted in October 2007 after the first interim analysis showed no evidence of vaccine efficacy:
  - No reduction in HIV-1 acquisition rates
  - No reduction in HIV-1 viral load set-point

---

1-tailed p-value = 0.044 (for $V_{INF} < 0$)
2-tailed p-value = 0.077 (for $V_{INF} \neq 0$)
Figure 2: Kaplan-Meier plots of HIV infection for male vaccine and placebo groups by baseline Ad5 antibody titre ≤18 (A); baseline Ad5 antibody titre between >18 and ≤200 (B); baseline Ad5 antibody titre between >200 and ≤1000 (C); and baseline Ad5 antibody titre >1000 (D).

Each hazard ratio (HR) is from a univariate Cox regression model.
Vacuna MSD: Step trial
Infecting HIV sequences Gag sequences differ genetically from sequences contained in the vaccine.
STEP trial post-analyses

- Viruses in breakthrough infections (i.e. in vaccine group) are genetically further apart from the vaccine sequence than viruses in the placebo-group.

- This “sieve-effect” suggests that:
  - the vaccine may have blocked the out-growth of HIV variants that were most similar to the vaccine
  - the vaccine induced immune response may have driven specific viral evolution

- The differences in viral evolution or strain selection did NOT affect viral load, but the observed selection effect indicates that the induced immunity was in some way acting on the virus at least.
Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine

Scott G. Hansen¹, Julia C. Ford¹, Matthew S. Lewis¹, Abigail B. Ventura¹, Colette M. Hughes¹, Lia Coyne-Johnson¹, Nathan Whizin¹, Kelli Oswald², Rebecca Shoemaker², Tonya Swanson¹, Alfred W. Legasse¹, Maria J. Chiuchiolo³, Christopher L. Parks³, Michael K. Axthelm¹, Jay A. Nelson¹, Michael A. Jarvis¹, Michael Platak Jr², Jeffrey D. Lifson² & Louis J. Picker¹
Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

Supachai Rerks-Ngarm, M.D., Punnee Pittisutthithum M.D., D.T.M.H., Sorachai Nitayaphan, M.D., Ph.D., Jaranit Kaewkungwal Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Premsri, M.D., Chawetsan Namwat, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stablein, Ph.D., Deborah L. Birx, M.D., Supamit Chunsuttiwat, M.D., Chirasak Khamboonruang, M.D., Prasert Thongcharoen, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kunasol, M.D., and Jerome H. Kim, M.D., for the MOPH–TAVEG Investigators*
Poxvirus (ALVAC)
α dominio interacción CD4

α dominio de fusión

Viral envelope

(Burton D. Human neutralizing antibodies and a vaccine for HIV-1. XIV International AIDS Conference [Abstract n°201])
Total of 16402 individuals enrolled between vaccine and placebo group.
Is there an early effect on HIV acquisition?

Efficacy (mITT)

<table>
<thead>
<tr>
<th>Cumulative # Infections</th>
<th>Placebo</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td>50</td>
<td>32</td>
<td>45</td>
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<tr>
<td>65</td>
<td>45</td>
<td>61</td>
</tr>
<tr>
<td>74</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P = 0.01

52,985 person-years
125 infections
Vaccine infections: 51
Placebo infections: 74

VE: 31.2%
p = 0.04
95% CI: 1.1, 52.1
(O’Brien-Fleming-adjusted)
> 99 %
Thai trial RV144

30 %
Comparison of Infection Rate and Vaccine Efficacy Between Vaccinees and Placebo Recipients in the RV144 ALVAC-HIV, VAXGEN Trial
Broadly Cross-Neutralizing Antibodies in HIV-1 Patients with Undetectable Viremia. Medina-Ramírez et al, J. Virology, in press

<table>
<thead>
<tr>
<th></th>
<th>V1 191 (A)</th>
<th>NL4-3 (B)</th>
<th>AC10 (B)</th>
<th>92BR025 (C)</th>
<th>92UG024 (D)</th>
<th>CM244 (E)</th>
<th>VSV</th>
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<tbody>
<tr>
<td>528-010</td>
<td>49.1±11.3</td>
<td>1.7±0.9</td>
<td>134±1.7</td>
<td>68±3.0</td>
<td>7.4±5.3</td>
<td>13.8±1.1</td>
<td>67.1±2.2</td>
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<tr>
<td>734-000</td>
<td>17.9±3.7</td>
<td>0.1±0.3</td>
<td>28.0±5.1</td>
<td>2.1±1.0</td>
<td>21.4±9.6</td>
<td>38.9±3.9</td>
<td>58.7±2.6</td>
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<tr>
<td>521-005</td>
<td>26.3±3.1</td>
<td>2.1±1.4</td>
<td>27.1±2.7</td>
<td>30.8±4.7</td>
<td>23.3±2.9</td>
<td>16.6±1.0</td>
<td>70.0±2.4</td>
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<td>600-003</td>
<td>28.1±3.5</td>
<td>3.1±0.7</td>
<td>44.2±8.2</td>
<td>13.1±5.0</td>
<td>42.5±21.9</td>
<td>22.9±0.8</td>
<td>54.1±6.6</td>
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<td>363-014</td>
<td>26.7±14.4</td>
<td>2.4±0.3</td>
<td>15.9±3.7</td>
<td>14.8±0.4</td>
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<td>541-011</td>
<td>34.9±4.0</td>
<td>4.5±0.5</td>
<td>46.2±6.0</td>
<td>26.3±1.8</td>
<td>46.4±2.7</td>
<td>48.5±2.7</td>
<td>62.6±4.8</td>
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<td>181-036</td>
<td>40.6±10.2</td>
<td>14.6±3.1</td>
<td>46.1±13</td>
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<td>488-013</td>
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<td>103.1±5.9</td>
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</table>
α dominio interacción CD4

α dominio de fusión

Viral envelope

(Burton D. Human neutralizing antibodies and a vaccine for HIV-1. XIV International AIDS Conference [Abstract nº201])
Thai trial RV144
Timelines Prophylactic Vaccines

T and B cell immunogens in:

**DNA Vectors**
- Murine analysis, immunogenicity & GMP + Toxicology
- Cloning & expression, Murine analysis & immunogenicity
- Phase I clinical trial

**MVA Vectors**
- GMP + Toxicology
- Loading & representation
- Phase I clinical trial

**HSP Vectors**
- Murine analysis, immunogenicity & GMP + Toxicology
- Phase I clinical trial

**BCG Vectors: rBCG:HIVA**
- rBCG-2auxo-HIVconsv, -HIVACAT T-cell, -malaria+TB
- Construction, stability & imm.
- BCG - synthesis vector for VLPs

**VLP**
- Murine analysis, Immunogenicity & GMP + Toxicology
- Phase I clinical trial

**RISVAC02- MVA**
- Phase I clinical trial & trial data
- Phase II clinical trial
- Prime/boost

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HIVACAT Current Period

- 2011
- 2012
- 2013
- 2014
- 2015
- 2016

HIVACAT Second Period

- 2011
- 2012
- 2013
- 2014
- 2015
- 2016
Timelines B cell immunogen

New neutralizing Ab
- Isolation of human monoclonal Ab

Immunogen design for nAb
- Library of mutant Env proteins
- Selection, phenotypic characterization and immunogenicity
- Studies of selected variants

Ab secreting cells in STI
- Patients screening
- Neutralization as.
- nAb identification

gp41 immunogens
- Immunogenicity
- Murine & stability analysis
- Design optimized strat. human immunization

Selected Env Seq. / nAb

HIVACAT Current Period
- 2011
- 2012

HIVACAT Second Period
- 2013
- 2014
- 2015
- 2016
1. General considerations

2. Therapeutic vaccines against HIV. Dendritic cells

3. Preventive vaccines against HIV. Other strategies for prevention

4. Final considerations
Efficacy of HIV Prevention Strategies From Randomized Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect Size, % (95% CI)</th>
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<td>ART for prevention; HPTN 052, Africa, Asia, Americas</td>
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<td>PrEP for discordant couples; Partners PrEP, Uganda, Kenya</td>
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<td>PrEP for heterosexual men and women; TDF2, Botswana</td>
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<td>Medical male circumcision; Orange Farm, Rakai, Kisumu</td>
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<td>PrEP for MSMs; iPrEX, Americas, Thailand, South Africa</td>
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<td>Sexually transmitted diseases treatment; Mwanza, Tanzania</td>
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<td>Microbicide; CAPRISA004, South Africa</td>
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<td>HIV vaccine; RV144, Thailand</td>
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</table>

The Research Centres

- Two internationally renowned centres of reference
- More than 60 investigators

Program Directors
Scientific Dr
HIVACAT Strategic Committee