THERAPEUTIC VACCINES (TV) & OTHER IMMUNE INTERVENTIONS (IBT) IN HIV INFECTION: 2013

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Therapeutic vaccines against HIV infection

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Keywords: therapeutic vaccine, dendritic cell, HIV, functional cure, recombinant virus, DNA

Immunological Reviews 2013

Guislaine Carcelain
Brigitte Autran

Immune interventions in HIV infection

CURRENT OPINION Vaccine and immunotherapeutic interventions

Giuseppe Pantaleo and Yves Lévy 2013
1. Where are we with ART

2. Untreated patients. TV/IBT to control productive HIV replication or restore CD4’s

3. TV/IBT in virologically suppressed patients with chronic HIV infection

4. TV to reduce the size of the reservoirs and/or to control already depleted reservoirs

5. Final considerations
FIG. Indetectabilidad por año sobre pacientes activos con al menos 1 año de TARGA (cv<400) Sobre la última carga viral disponible en cada año de cada paciente.

FIG. Exitus por año sobre pacientes activos.
Inflammation
Immuneactivation
Accelerated aging/comorbidities
Residual replication
Latent infection
Long life

* Often a convenient, single pill & well tolerated regimen
SPANISH EARTH-1 STUDY (CD4>500 AND VL >10000). STOP THERPAY AFTER 1 YEAR OF D4T+3TC+RIT/IND AND VL<20

D4T+3TC+RIT

D4T+3TC+RIT/IND

STOP

HIV-1 RNA COPIES/ML

Garcia F et al AIDS, 1999
1. Where are we with ART

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2. Untreated patients. TV/IBT to control productive HIV replication or restore CD4’s

**Biological model:**
Capacity of the immune system (HIV-specific CTL’s and T-helper cells) to partially control viral replication in HIV natural infection and establishing a viral set point lower than peak viremia

**Potential objectives:**
Replace ART
Partially replace ART (less drugs)
Delay ART
IL-2

GSK-biologicals 732426

Passive transfer of Abs

Autologous dendritic cells based vaccines pulsed with inactivated (AT2, heat) autologous virus
Figure 2. Comparison of virus rebound in acutely infected subjects with and without passive immunization. (a) Control group of subjects with acute HIV infection undergoing treatment interruption; viral load profiles of 12 subjects who initiated ART during acute infection and subsequently underwent treatment interruption without receiving antibody treatment are shown. Viral load is the log HIV RNA copies/ml in plasma. The dotted line indicates the detection limit. (b) Time until rebound of viremia (first time viral load detectable at >10 RNA copies/ml, increase over day 0 value) was determined in the control group and in acutely infected subjects who received passive immunization. The fraction of subjects without rebound at a given time point was compared using Kaplan-Meier curves and log rank test. One data point (subject NAB14, week 24) was censored because rebound had not occurred in this patient.

(data not shown). Overall, plasma levels of 2G12 were significantly higher than those of 2F5 or 4E10 (Dunn multiple comparison test, $P < 0.001$ and $P < 0.01$, respectively). Of note, plasma concentrations of 2G12 and the sensitivity of the subjects’ pretrial isolates to inhibition by 2G12 were higher amongst responders, whereas no significant difference in these parameters was found for 2F5 and 4E10 (Fig. 4c,d). To estimate what range of antibody concentrations are required to
Therapeutic dendritic-cell vaccine for chronic HIV-1 infection
Wei Lu, Luiz Claudio Arraes, Wylla Tatiana Ferreira & Jean-Marie Andrieu
Inclusion criteria:
1. VL > 10000 c/ml
2. CD4 >450 c/mm³
3. Off cART

A therapeutic dendritic cell-based vaccine for HIV-1 infection.
García F et al J Infect Dis 2011;203:473-8

VIRUS CULTURE 10x9

1st 2nd 3rd doses of pulsed MD-DC 10x7

DC-HIV (N=12)

Blood sample (120 ml) for DC generation

DC-PLACEBO (N=12)

48 WEEKS

A Therapeutic Dendritic Cell-Based Vaccine for HIV-1 Infection
Felipe Garcia,1 Nuria Clement,1 Lambert Assoumou,6 Cristina Gil,1 Nuria González,2 José Alcamí,3 Agathe León,1 Joan Romeu,1 Judith Dalmau,5 Javier Martínez-Picado,2,5 Jeff Lifson,6 Brigitte Autran,2 Dominique Costagliola,6 BonaventuraClotet,4,5 Josep M Gatell,1 Montserrat Plana, and Teresa Gallart,1 for the DCV2/MANON07- AIDS Vaccine Research Objective Study Group*. JID, 2011
IT WAS OBSERVED A MODEST DECREASE OF VL IN VACCINATED PATIENTS.
1. Where are we with ART

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2. TV/IBT in virologically suppressed patients with chronic HIV infection

**Biological model:**
Many infectious diseases (TB, Toxo, H Zoster ...)
HIV elite controllers

**Potential objective:**
Plasma VL BLQ without life long ART (functional cure)
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.
CTL’s

plasma viral load

Control/escape

EC (1-3%)
plasma viral load

HAART

TV

STOP HAART

months

5 10 15 20 25 30 35 40 45 50 55 60
Viral vectors based vaccines (poxviruses, adenoviruses, ....)

Replicative viral vectors based vaccines (herpesviruses .....)

Autologous dendritic cells based vaccines pulsed with .......

Other modalities (proteins, peptides) / combinations

Passive transfer of nAbs
Greater viral rebound and reduced time to resume antiretroviral therapy after therapeutic immunization with the ALVAC-HIV vaccine (vCP1452)

Brigitte Autrana,b,c, Robert L. Murphyd,e,f, Dominique Costagliola,d,e,g, Roland Tubiana2,d,e,g, Bonaventura Cloteth, Jose Gatelli, Schlomo Staszewskij, Norma Winckerk, Lambert Assoumoue,g, Raphaëlle El-Habibl, Vincent Calvez2,m,n, Bruce Walkero, Christine Katlama2,d,e,g and the ORVACS Study Group

Graph showing the change in plasma HIV-1 RNA levels over time for different groups receiving different numbers of ALVAC injections (3 vs. 4) and a placebo group.
Safety, Immunogenicity and Dynamics of Viral Load Rebound After cART Interruption in Chronic HIV Infected Patients Receiving MVA-B Vaccination

Beatriz Mothe1, Nuria Climent2, Montserrat Plana2, Miriam Rosas1, José Luis Jiménez3, María Angeles Muñoz-Fernández3, Judit Pich2, Joan Albert Arnaiz2, Jose M Gatell2, Bonaventura Clotet1, Mariano Esteban4, Juan Carlos López Bernaldo de Quirós3, Felipe Garcia2 and Christian Brander1 for the RISVAC-03 Study.

1. Irsicaixa-HIVACAT, Hospital Germans Trias i Pujol, Badalona, Spain
2. Hospital Clinic-HIVACAT, IDIBAPS, University of Barcelona, Spain
3. Hospital Gregorio Marañón, Madrid, Spain
4. Centro Nacional de Biotecnología, Madrid, Spain
VL rebound after analytical treatment interruption in MVA-B (n=11) vs placebo (6) recipients

**Vaccine**

**Placebo**

**AUC Week 4**

\[ p = 0.02 \]
AIDS Clinical Trials Group 5197: A Placebo-Controlled Trial of Immunization of HIV-1–Infected Persons with a Replication-Deficient Adenovirus Type 5 Vaccine Expressing the HIV-1 Core Protein

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 Piatak Jr², Jeffrey D. Lifson² & Louis J. Picker¹

C

Group A (CMV/CMV)  
\(n = 6\)  
\(P = 0.0017\)

Group B (CMV/Ad5)  
\(n = 5\)  
\(P < 0.0001\)

Group C (DNA/Ad5)  
\(n = 9\)

Group D (controls)  
\(n = 27\)  
\(n = 1\)
DCs have a central role in HIV infection. The initial contact of HIV-1 with DCs can result in opposite outcomes:

- Beneficial in inducing strong HIV-specific T-cell responses
- Detrimental in promoting the dissemination of HIV-1 and/or immunotolerance

GENERACIÓ DE LA VACUNA
Extracció d'una mostra de sang per a l'obtenció de DCs
Aïllament dels monòcits i diferenciació ex vivo a DCs
Virus autòlegs obtinguts per plasmafèresis
Pulsing dels virus i les DCs autòlegs
Obtenció de la vacuna terapèutica
• Different immunogens (load or pulse):
  • autologous inactivated virus (heat, AT-2)
  • HIV-1 proteins
  • Peptides
  • mRNA
  • recombinant virus vectors nanoparticles
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

Received 29 September 2004; accepted 3 December 2004; electronically published 11 April 2005.

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The Journal of Infectious Diseases 2005; 191:1680–5
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0022-1899/2005/19110-0014$15.00
**DCV-1 study**

**Figure 3A**

Cases: n=12

**Figure 3B**

Patient #262

**Figure 3C**

Patient #207

**Figure 3D**

Controls: n=4

Weeks after HAART interruption

log$_{10}$ of plasma viral load (copies/ml)
High dose virus and MD-DCs in patients on cART
A Dendritic Cell–Based Vaccine Elicits T Cell Responses Associated with Control of HIV-1 Replication

Felipe García, Nuria Climent, Alberto C. Guardo, Cristina Gil, Agathe León, Brigitte Autran, Jeffrey D. Lifson, Javier Martínez-Picado, Judit Dalmau, Bonaventura Clotet, Josep M. Gatell, Montserrat Plana, Teresa Gallart, For the DCV2/MANON07-ORVACS Study Group

Combination antiretroviral therapy (cART) greatly improves survival and quality of life of HIV-1–infected patients; however, cART must be continued indefinitely to prevent viral rebound and associated disease progression. Inducing HIV-1–specific immune responses with a therapeutic immunization has been proposed to control viral replication after discontinuation of cART as an alternative to “cART for life.” We report safety, tolerability, and immunogenicity results associated with a control of viral replication for a therapeutic vaccine using autologous monocyte-derived dendritic cells (MD-DCs) pulsed with autologous heat-inactivated whole HIV. Patients on cART with CD4+ ≥450 cells/mm³ were randomized to receive three immunizations with MD-DCs or with nonpulsed MD-DCs. Vaccination was feasible, safe, and well tolerated and shifted the virus/host balance. At weeks 12 and 24 after cART interruption, a decrease of plasma viral load setpoint ≥1 log was observed in 12 of 22 (55%) versus 1 of 11 (9%) and in 7 of 20 (35%) versus 0 of 10 (0%) patients in the DC-HIV-1 and DC-control groups, respectively. This significant decrease in plasma viral load observed in immunized recipients was associated with a consistent increase in HIV-1–specific T cell responses. These data suggest that HIV-1–specific immune responses elicited by therapeutic DC vaccines could significantly change plasma viral load setpoint after cART interruption in chronic HIV-1–infected patients treated in early stages. This proof of concept supports further investigation of new candidates and/or new optimized strategies of vaccination with the final objective of obtaining a functional cure as an alternative to cART for life.
Inclusion criteria:
1. <20 copies/ml
2. Nadir >350 C
3. CD4+ T c/mm³

-72  -32  -24  0  2  4  6  8  10  48  WEEK

STOP 1
Virus culture
Doses of pulsed MD-DC

STOP 2

ARM III (N=12)

ARM IV (N=12)

ARM V
CONTROL GROUP (N=12)

Blood sample (120 ml) for DC generation

Doses of pulsed MD-DC

Doses of NON-pulsed MD-DC

DCV2-b study

HAART
Stop HAART
Figure 2A

![Graph showing changes in Δ Log 10 PVL (copies/ml) over weeks for DC-HIV-1 and DC-CONTROL.](image)

- **DC-HIV-1**
  - Weeks: 24, 23, 22, 21, 20, 17

- **DC-CONTROL**
  - Weeks: 11, 11, 11, 10, 9, 6

- AUC: P = 0.04
CHANGES IN IFN-γ PRODUCING HIV SPECIFIC T CELLS

ΔSFC/10⁶ PBMC

DC-HIV-1
DC-CONTROL

CTL response

*p=0.045

*p=0.001

*p=0.001

*p=0.001

ΔLog 10 pVL (copies/ml)

* p=0.05

* p=0.001

CHANGES IN IFN-γ PRODUCING HIV SPECIFIC T CELLS
CONCLUSIONS

- Therapeutic vaccination was feasible, safe and well tolerated.
- A consistent and significant decrease in VL (1 log) was observed in vaccine recipients and was correlated with an increase in CD4 T cell count.
- 86% of vaccinated patients had a significant lower set point VL when compared to baseline and this was maintained in 52% of patients at week 48.
Editor’s Summary:
Putting the Vaccine Before the cART

Combination antiretroviral therapy has turned HIV infection from a death sentence to a manageable disease. However, current treatment requires “cART for life,” a less than ideal situation for HIV-infected individuals because of drug cost and worries about resistance. New vaccine strategies are attempting to control viral replication after infection, thus allowing discontinuation of cART and a “functional cure.” Garcia et al. report a dendritic cell (DC)–based vaccine that elicits an HIV-1–specific immune response and may change the setpoint of viral load. The authors pulsed the patient’s own DCs with heat-inactivated whole HIV and then used these DCs as a therapeutic vaccine. The vaccine was safe and well tolerated. They observed a decrease in viral setpoint after cART interruption in vaccinated patients with a concomitant increase in HIV-1–specific T cell responses. Although not yet a functional cure, these results support future studies optimizing a therapeutic vaccine to maintain HIV-1–infected patients.
Pre-ART plasma banking:
- Small amounts of plasma
- Leukapheresis
- Intradermal injection

AGS-004 immunotherapy:
- HIV-1 virus
- Virus RNA
- Amplified RNA
- Monocytes
- Partially mature dendritic cell
- Vial and freeze
- Mature dendritic cell
- Partially mature dendritic cell

Routy, Nicolette Immunotherapy. 2010
Pre-ART vs. Week 12 of STI Log Change in Viral Load
Phase 2b Study Schematic: Chronic Cohort*:
USA and Canada

Involving participants from private community medical clinics

Global PI: J M. Jacobson
Phase 2b data expected mid 2014

*All patients were chronically infected for more than 6 months prior to initiating ART
iHIVARNA
The iHIVARNA consortium

Academic partners

Non-academic partners

Regulatory affairs

Administrative coordinator

SME (mRNA production)

SEVENTH FRAMEWORK PROGRAMME
Concept of iHIVARNA

**Intranodal vaccination of HIV-1 infected patients with mRNA encoding TriMix and HIVACAT**

**Activation signals: TriMix**

**Antigen: HIVACAT**

**In situ DC modification** ➔ HIV-1 specific T-cell responses
THERAPEUTIC VACCINES (TV) & OTHER IMMUNE INTERVENTIONS (IBT) IN HIV INFECTION: 2013

1. Where are we with ART

2. Untreated patients. TV/IBT to control productive HIV replication or restore CD4´s

3. TV/IBT in virologically suppressed patients with chronic HIV infection

4. TV/IBT to reduce the size of the reservoirs and/or to control already depleted reservoirs

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THERAPEUTIC VACCINES (TV) & OTHER IMMUNE INTERVENTIONS (IBT) IN HIV INFECTION: 2013

2. TV/IBT to reduce the size of the reservoirs and/or to control already depleted reservoirs

**Biological model (functional cure)**

Visconti patients

**Reservoirs can be reduced (purged ?):**

- ART alone early after PHI
- ART + TV ?
- ART+ mobilizing agent + TV ?
The VISCONTI cohort: the possibility of post-treatment control

Capacity of CD8+ T cells to suppress HIV infection of CD4+ T cells
Determined by log-fold decrease in the level of secreted p24 (CD4 vs CD4:CD8 1:1 cell cultures).

Evolution of cell-associated HIV DNA after treatment interruption in PBMCs from 8 PTCs.
Left: five PTCs experienced a decline in their cell-associated HIV DNA levels
Right: two PTCs maintained stable levels and a positive slope was calculated for OR3
Very early treatment in adults: restricted reservoir formation?

**Acute HIV**

- Median integrated HIV DNA copies/10^6 PBMC
- Fiebig I: 24
- Fiebig III: 36
- Undetectable integrated HIV DNA: 92% 53%

**1 year cART**

- Median integrated HIV DNA copies/10^6 PBMC
- Fiebig I: 11
- Fiebig III: 18
- Undetectable integrated HIV DNA: 100% 89%

DC vaccine and HIV reservoir

AGS-004 DC dosing:

- Total Subjects (N=29)
  - Mean (SD)

- Age: 39.27 (8.60)
- Pre-ART CD4+ T cell nadir (cells/mm³): 306.5 (137.1)
- Log Pre-ART HIV-1 RNA (copies/mL): 4.91 (0.59)
- Baseline CD4+ T cell (cells/mm³): 637.3 (203.9)
- Duration of ART (years): 3.14 (2.11)

Study weeks:
- Screening: 0
- 4
- 8
- 12
- 16
- 20
- 24
- 26

Sample collection: available, N
- 20
- DNA sampling

8 clinical sites in Canada:
Including 3 private community medical centres

Tcherepanova et al. PO4.35 LB AIDS vaccine 2013
Pro viral DNA change (%) at week 14 vs. week 0 after 4 doses of AGS-004 on ART

percent change DNA in CD4 T cells

*Significant change when > 1.3 fold change (28%) based on inter assay variability

Tcherepanova et al. PO4.35 LB AIDS vaccine 2013
AGS-004-003 Acute infection study
Uncontrolled, Open Label

AGS-004 dosing

Study weeks 0 4 8 12 16 20 24 28 30

*Immune response evaluation

*AHI=acute HIV infection initiated ART within 45 days of primary infection

PI: DM Margolis
6 patients recruited
Combination Strategies To Purge The HIV Reservoir

Yves Levy

Latent Reservoir
$T_{CM}/T_{TM}$ CD4 cells

- Reactivation of replication
- HDAC Inhibitors, SAHA, Prostratin, Bryostatin 1, 5-azathidine, anti-PD-1
- Inhibitors of immune activation

Therapeutic vaccine, anti-PD-1, Cytokines (IL-2, IL-7), Inhibitors of immune activation

Killing by effector CD8 T cells

APOPTOSIS

Covert Cellular Reservoir
with Residual Replication

- Potentiation of immune response
- Selective targeting
- Antibody coupled with toxins

G. Pantaleo, IAS HIV cure, 2012
Disulfiram Reactivates Latent HIV-1 without Inducing T Cell Activation

But it is not yet clear that disulfiram can reactivate latent HIV-1 in vivo

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Treatment Time Course (days)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Media Alone</td>
<td>67</td>
</tr>
<tr>
<td>Disulfiram 0.4 μM</td>
<td>UD</td>
</tr>
<tr>
<td>anti-CD3 + anti-CD28</td>
<td>49</td>
</tr>
</tbody>
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Rome, July 20, 2011

Dynamics of Viral Load (VL) Rebound After cART Interruption in Chronic HIV Infected Patients Receiving MVA-B plus Disulfiram.

Beatriz Mothe1, Sonsoles Sánchez2, Saray Corral3, Nuria Climent2, Alberto C. Guardo2, Lorna Leal2, Berta Torres2, José Luis Jiménez3, Judit Pich2, Joan Albert Arnaiz2, Agathe León2, María Ángeles Muñoz-Fernández3 , Jose M Gatell2, Bonaventura Clotet1, Mariano Esteban4, Montserrat Plana2, Juan Carlos López Bernaldo de Quirós3, Christian Brander1, Felipe García2 for the RISVAC-03 Study.

1. Irsicaixa-HIVACAT, Hospital Germans Trias i Pujol, Badalona 2. Hospital Clinic-HIVACAT, IDIBAPS, University of Barcelona 3. Hospital Gregorio Marañón, Madrid 4.- Centro Nacional de Biotecnología, Madrid. Spain
**Clinical Trial Design**

**ARM A: VACCINE/PLACEBO ARM (n=18, randomized 2:1)**

- V0
- w2
- w4
- w6
- w8
- w16
- w18
- w24
- w36

**ARM B: VACCINE/PLACEBO + MOBILIZERS (n=12)**

- V0
- w2
- w4
- w6
- w8
- w16
- w18
- w24

**Immunogenicity measurements:** baseline, 2w post 2nd and 3rd vaccine and w24

**Reservoirs mobilizers:** DISULFIRAM

**Chronic HIV-1 inf documented HAART supressed**

**Treatment interruption**

**cART re-start**

**MVA-B**

**END OF TRIAL**
Viral load rebound after vaccination vs vaccination plus disulfiram. Absolute numbers and changes as compared with baseline viral load before any cART.
Barouch et al. Nature 2013
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- HIV therapeutic vaccines may play a role to overcome some of the limitations of ART
  
  Delay or avoid VL rebound after ART interruption
  Deplete the reservoirs
  Purge the reservoirs shock & kill strategies

- Most promising results so far, in humans, have been obtained with dendritic cells based therapeutic vaccines
HIVACAT
Projecte de Recerca de la Vacuna de la Sida