INTRODUCTION TO HIV PATHOPHYSIOLOGY

ROGER PAREDES
MD, PHD

INFECTIOUS DISEASES SERVICE & IRSICAIXA AIDS RESEARCH INSTITUTE
HOSPITAL UNIVERSITARI GERMAN TRIAS I PUJOL
BADALONA, CATALONIA, SPAIN
DISCLOSURES

- I have received research grants from MSD, ViiV and Gilead
- I have participated in advisory boards for MSD and ViiV
- I don’t have stock options
Recent: 0 - 6 months
Main symptoms of Acute HIV infection

**Systemic:**
- Fever
- Weight loss

**Central:**
- Malaise
- Headache
- Neuropathy

**Pharyngitis**

**Mouth:**
- Sores
- Thrush

**Esophagus:**
- Sores

**Muscles:**
- Myalgia

**Liver and spleen:**
- Enlargement

**Lymph nodes:**
- Lymphadenopathy

**Skin:**
- Rash

**Gastric:**
- Nausea
- Vomiting
Life Expectancy for 20-Year-Old Newly Diagnosed with HIV, 1980s and Today

1980s (no ART) 1-2 years from AIDS diagnosis

Today (on ART) ~53 years

Source: JL Marcus et al., JAIDS, 2016.
HIV LIFE CYCLE AND ART
VIRAL LOAD FOLLOWING TREATMENT INTERRUPTION

- N=8
- **ART started at Fiebig I** (HIV RNA+, p24 Ag-, Ab-) for ≥ 96 w.
- VL <50 c/mL ≥48 w & CD4 >400 cells.
- Resume ART if two VL >1000 c/ml or two CD4 <350 cells.
- TI for 24 w. VL every 3-7 days.

**Hypothesis.**
- At least 30% of individuals will have delayed time to VL rebound (VL<50 at 24 w).
- Proceed to stage 2 if ≥ 1 person has VL <50 c/ml at week 12.

**Median time to viral rebound:** 26 days (range 13-48)
**Highest VL at rebound** (median): 5169 (2005 – 13462)
HIV is the greatest escapist
HIV-1 Strategies to counteract host immunity
HUGE GENETIC DIVERSITY

Population level

Individual level

Deep sequencing

Sanger sequencing
• **Balance between mutation rate, drift and selection**

1. High replication rate: $10^{9-12}$ new virions/day
2. Error-prone polymerase:
   - 1 mutation / 10,000 bp
   - 3-8 recombination events / mutation event
3. Cellular mechanisms: MDR1 gene codes for P-glycoprotein
4. Role of RNAseH
5. Selective pressure of Abs & CTLs against HIV epitopes
6. Viral pool size and availability of target cells
QUASISPECIES

“A population of viruses that share a common origin but which have distinct genomic sequences as a result from mutation, drift and the impact of selection”
In ARV-naïve subjects chronically infected with a “wild-type” HIV-1

- All non-deleterious single mutants likely preexist
- Few double mutants preexist
- Almost no triple mutants are expected
Pressure I
Pressure 1

Stop pressure

Pressure 2
Stop pressure
DIVERSITY

Mutation rate

Drift

Selection
Drift
HLA-I molecules are a major driving force of HIV-1 evolution
CD8+ T-cell responses and HIV-1 escape
HLA class I alleles are also highly diverse
Host HLA genetics and HIV diversity: frequent transmission of escaped epitopes and epitope loss over time
Broadly Neutralizing Antibodies Binding to Neutralization Epitopes on HIV Trimer

N332 Glycan Supersite
PGT121, PGT128, 10-1074

CD4 Binding Site
VRC01, PG04, CH31, 3BNC117, 12A12, CH103, VRC07-523, N6

V1V2 Apex
PG9, PG16, CH01-04, PGT141-45, PGDM1400, CAP256-VRC26

Trimer Interface
8ANC195, PGT151, 35022, VRC34, ACS202

gp41 MPER
2F5, 4E10, 10E8

Cryo-EM of viral spike by Subramaniam group. Fit with atomic level structures from Kwong and Wilson group.

Courtesy of John Mascola
GP160 FROM THE OUTSIDE
RESTRICTION FACTORS
QUASISPECIES AS A SURVIVAL STRATEGY

[Diagram showing viral load over time with stages labeled: acute infection, chronic infection, successful ART, therapy failure, treatment interruption, 2nd ART + failure. The figures show variants of wild-type HIV-1 and variants of drug-resistant HIV-1 with a level of resistance.]
HIV INFECTION DAMAGES THE GALT

HIV-          HIV+

% CD4+ T-cells

MICROBIAL TRANSLOCATION IN HIV
MICROBIAL TRANSLOCATION IN HIV PATHOGENESIS

Marchetti et al. Clin Microbiol Rev. 2013
Bacterial translocation and clinical progression

Microbial translocation predicts disease progression of HIV-infected antiretroviral-naive patients with high CD4+ cell count.


ICONA Cohort
- Documented last HIV-negative test and first HIV-positive
- Plasma sample stored while ART-naive
N=379.

Circulating LPS in the first year of infection is a good predictor of progression

MICROBIOME IN HIV

Guillén et al. Mucosal Immunology 2018
DYSBIOSIS BY GENE RICHNESS

Guillén et al. Mucosal Immunology 2018
LOW MICROBIAL GENE RICHNESS LINKED TO NADIR CD4

Gene richness by nadir CD4+ T-cell counts

χ² p-value = 0.002

Guillén et al. Mucosal Immunology 2018
MICROBIOME IN HIV
MICROBIOME IN HIV

Guillén et al. Mucosal Immunology 2018
VAGINAL DYSBIOSIS RECOGNIZABLE AS COMMUNITY-TYPES

Srinivasan et al. 2012

Anahtar et al., Immunity, 2015

Young women in SA have high vaginal microbial diversity
889 analysed in CAPRISA 004 tenofovir gel trial

157 were excluded
157 did not provide consent to use stored sample for research

732 cervicovaginal lavage samples evaluated

44 were excluded
29 failed QC by cluster analysis
13 had no microbial proteins detected
2 failed MS run alignment

688 participants analyzed

345 were in the group assigned to tenofovir gel

343 were in the group assigned to placebo gel

205 (59.4%) Lactobacillus group
140 (40.6%) non-Lactobacillus

9 acquired HIV infection
14 acquired HIV infection

202 (58.9%) Lactobacillus group
22 acquired HIV infection

141 (41.1%) non-Lactobacillus
17 acquired HIV infection

Klatt et al., Science 2017
**A. Lactobacillus dominant**

Efficacy, 61%
95% CI, 11 to 84%

**B. Non-Lactobacillus dominant**

Efficacy, 18%
95% CI, -77 to 63%

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<thead>
<tr>
<th></th>
<th>Lactobacillus dominant</th>
<th>non-Lactobacillus dominant</th>
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<tbody>
<tr>
<td></td>
<td>Tenofovir</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong># HIV-1 infections</strong></td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td><strong>HIV-1 incidence per 100 person-years</strong></td>
<td>2.7</td>
<td>6.9</td>
</tr>
<tr>
<td><strong>HIV-1 protection effectiveness</strong></td>
<td><strong>61%</strong> (11, 84), <em>p</em>=0.013</td>
<td><strong>18%</strong> (-77, 63), <em>p</em>=0.644</td>
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TDF DEPLETED BY GARDENERELLA BUT NOT LACTOBACILLUS

4 hours:
- G. vag vs Abiotic: P<0.0001
- G. vag vs. L. iners: P=0.0037
- G. vag vs. L. crisp: P=0.0019
- L. iners vs L. crisp: P=ns

24 hours:
- G. vag vs Abiotic: P<0.0001
- G. vag vs. L. iners: P<0.0001
- G. vag vs. L. crisp: P<0.0001
- L. iners vs. L. crisp: P=ns

Klatt et al., Science 2017
TDF METABOLISED TO ADENINE

TFV Metabolite formation

Adenine (mg/mL)

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Abiotic</th>
<th>L. iners</th>
<th>L. crispatus</th>
<th>G vaginalis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0001</td>
<td>0.0001</td>
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<tr>
<td>10</td>
<td>0.02</td>
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<tr>
<td>20</td>
<td>0.04</td>
<td>0.04</td>
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<td>0.04</td>
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<tr>
<td>30</td>
<td>0.08</td>
<td>0.08</td>
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Total Drug Recovery

TFV+Adenine

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<th>Time (hours)</th>
<th>Abiotic</th>
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<th>L. crispatus</th>
<th>G vaginalis</th>
</tr>
</thead>
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<tr>
<td>0</td>
<td>100</td>
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<td>30</td>
<td>40</td>
<td>40</td>
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4 hours:
- G. vag vs Abiotic: P<0.0001
- G. vag vs L. iners: P<0.0001
- G. vag vs L. crispatus: P<0.0001
- L. iners vs L. crispatus: P=0.02

24 hours:
- G. vag vs Abiotic: P=ns
- G. vag vs L. iners: P=ns
- G. vag vs L. crispatus: P=ns
- L. iners vs L. crispatus: P=ns

Klatt et al., Science 2017
MULTIPLE BV BACTERIA (BUT NOT LACTOBACILLUS) CAN METABOLIZE TENOFOVIR

24 hours:
P. amnii vs Abiotic (NYCIII): $P=0.0007$
P. bivia vs Abiotic (NYCIII): $P=0.0007$
M. mulierius vs Abiotic (NYCIII): $P=0.0007$
E. coli vs Abiotic (TS): $P=0.1000$

*Klatt et al., Science 2017*
EXTENSIVE IMPACT OF NON-ANTIBIOTIC DRUGS ON HUMAN GUT BACTERIA
MICROBIOME IN CANCER

Gopalakrishnan et al, Cancer Cell 2018
TROPSIM PREDICTION

- **X4 (SI)**
- **Dual tropic**
- **R5 (NSI)**

**T-cell lines**
- CD4
- CXCR4

**Primary lymphocytes**
- CD4 Naïve
- CCR5

**Monocyte/macrophages**
- CD4 memory
TROPISM

Rate of progression to CD4+ < 350, initiation of ART or death

Logrank = 5.85  p = 0.0156

Goetz. JAIDS 2009
TIME OF X4 VIRUS EMERGENCE IN RELATION TO CD4 INFLECTION POINT

Shepherd. MACS cohort, JID 2008
TROPISM & CD4 LOSS BEFORE ART

Waters CID 2008
TROPISM & CD4 GAIN AFTER ART

Waters CID 2008
WHY DO WE NEED TO CURE HIV?

- Life expectancy remains reduced on cART
- Ongoing morbidity on cART
- Prevent HIV transmission
- Substantial stigma and discrimination
- Lifelong cART:
  - adherence
  - toxicity
  - long term-cost

Estimated 2015 AIDS investment for universal prevention, treatment, care and support

22 billion USD

BARRIERS TO CURE HIV INFECTION

Where is the virus and how is it maintained in the face of suppressive therapy?

Residual replication

inflammation
immune activation

Latent infection
## HIV CURE: 2-MODELS

<table>
<thead>
<tr>
<th>Eradication</th>
<th>Remission</th>
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<tr>
<td>Sterilizing cure</td>
<td>Functional cure</td>
</tr>
<tr>
<td>Elimination of all HIV-infected cells</td>
<td>Long-term health without cART</td>
</tr>
<tr>
<td>HIV RNA &lt; 1 cop/mL</td>
<td>HIV RNA &lt;50 cop/mL</td>
</tr>
<tr>
<td>Berlin Patient post-BMT</td>
<td>Elite controllers Post-cART controllers</td>
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STRATEGIES TO CURE HIV

- Sterilizing Cure or Life-long Remission
- Treatment optimization & intensification (eliminate all replication)
- Reversal of HIV latency (increase viral production)
- Immune-based therapies (reverse pro-latency signaling)
- Therapeutic vaccination (to enhance host-control)
- Gene therapy
ICISTEM CONSORTIUM

International collaboration to guide and investigate the potential for HIV cure in HIV-infected patients requiring allogeneic stem cell transplantation for hematological disorders

**AIM 1**
To guide clinicians involved in allogeneic SCT procedures in HIV infected individuals

**AIM 2**
To better understand the underlying biological processes leading to viral reservoir reduction and potential cases of HIV-1 eradication/remission.

**Current Status**
40 individuals transplanted. ATI in 2 who received CCR5Δ32 cells (sep 2017 and nov 2018) without viral rebound. ATI with intervention for 5 individuals transplanted with wildtype cells is being prepared.

**Principal Investigators:**
Javier Martinez Picado
Annemarie Wensing

www.icistem.org
CONCLUSIONS

• HIV is the great scapist
  – Diversity
    • HIV
    • HLA
  – Integrated DNA
  – Env glycosylation
  – GALT damage
  – Inflamaging
Thanks for the slides to:
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Júlia Garcia-Prado
Ester Ballana
Josep Maria Llibre