Future Challenges of HIV treatment

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Future Challenges of HIV treatment

• State of the ART

• Perfecting ART

• Treatment as prevention

• Cure
ART in 2016

• Start at any CD4 cell counts
• 29 approved drugs
  • 5 broad mechanistic classes: NRTI, NNRTI, PI, INSTI, EI
• Up to 10 recommended first-line regimens
  • 1 standard strategy: 2 NRTI + [NNRTI, PI, or INSTI]
• Properties
  • Virologic activity
  • Safety and tolerability
  • Convenience
  • Access and cost
  • Life Expectancy
  • Treatment as Prevention
## When to Start? 2016

<table>
<thead>
<tr>
<th></th>
<th>AIDS/symptoms</th>
<th>CD4 &lt;200</th>
<th>CD4 200-350</th>
<th>CD4 350-500</th>
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<tr>
<td><strong>US DHHS 2016</strong></td>
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<td><a href="http://www.bhiva.org">www.bhiva.org</a></td>
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<td>strongly recommended</td>
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*PRIORITY*
Antiretroviral Drug Approval: 1987 - 2016
# ART: What to Start? Recommended/Preferred

<table>
<thead>
<tr>
<th>ART Institution</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>II</th>
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</thead>
<tbody>
<tr>
<td><strong>US DHHS 2016</strong>&lt;br&gt;www.aidsinfo.nih.gov</td>
<td>TAF/FTC&lt;sup&gt;Δ&lt;/sup&gt; TDF/FTC ABC/3TC&lt;sup&gt;+&lt;/sup&gt;</td>
<td>--</td>
<td>DRV/r</td>
<td>DTG, EVG, RAL</td>
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<td><strong>IAS-USA 2014</strong>&lt;br&gt;JAMA 2014;312:390</td>
<td>TDF/FTC ABC/3TC&lt;sup&gt;*&lt;/sup&gt;</td>
<td>EFV RPV&lt;sup&gt;*&lt;/sup&gt;</td>
<td>ATV/r DRV/r</td>
<td>DTG, EVG, RAL</td>
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<td>TDF/FTC ABC/3TC&lt;sup&gt;+&lt;/sup&gt;</td>
<td>RPV&lt;sup&gt;*&lt;/sup&gt;</td>
<td>DRV/r</td>
<td>DTG, EVG, RAL</td>
</tr>
<tr>
<td><strong>UK 2015</strong>&lt;br&gt;www.bhiva.org</td>
<td>TDF/FTC</td>
<td>RPV&lt;sup&gt;*&lt;/sup&gt;</td>
<td>ATV/r DRV/r</td>
<td>DTG, EVG, RAL</td>
</tr>
<tr>
<td><strong>WHO 2015</strong>&lt;br&gt;<a href="http://www.who.int/hiv/pub/guidelines/en/">http://www.who.int/hiv/pub/guidelines/en/</a></td>
<td>TDF + 3TC or FTC</td>
<td>EFV</td>
<td>--</td>
<td>DTG**</td>
</tr>
</tbody>
</table>

<sup>Δ</sup> only in combination with FTC/EVG/c  
<sup>+</sup> only with DTG  
** Option
Life Expectancy: ART - UK CHIC (2000-2012)
Expected age of death at 35 yo
N=21388 starting ART

MEN

WOMEN

May AIDS 2014;28:1193
Prevention of HIV-1 Infection with Early Antiretroviral Therapy

HPTN052: Linked Transmission

Total HIV-1 transmission events: 39

Linked transmissions: 28
  - Immediate arm: 1
  - Delayed arm: 27

Unlinked or TBD transmissions: 11
  - 18/28 (64%) transmissions from infected participants with CD4 > 350 cells/mm$^3$
  - 23/28 (82%) transmissions in sub-Saharan Africa
  - 18/28 (64%) transmissions from female to male partners

Cohen M, et al. IAS 2011; Presentation MOAX0102
The New England Journal of Medicine

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Volume 331 NOVEMBER 3, 1994 Number 18

REDUCTION OF MATERNAL-INFANT TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 WITH ZIDOVUDINE TREATMENT

Edward M. Connor, M.D., Rhoda S. Sperling, M.D., Richard Gelber, Ph.D., Pavel Kiselev, Ph.D., Gwendolyn Scott, M.D., Mary Jo O'Sullivan, M.D., Russell VanDyke, M.D., Mohammed Bey, M.D., William Shearer, M.D., Ph.D., Robert L. Jacobson, M.D., Eleanor Jimenez, M.D., Edward O'Neill, M.D., Brigitte Bazin, M.D., Jean-François Delfraissy, M.D., Mary Culnane, M.S., Robert Coombs, M.D., Ph.D., Mary Elkins, M.S., Jack Moyer, M.D., Pamela Stratton, M.D., and James Balsley, M.D., Ph.D., for the Pediatric AIDS Clinical Trials Group Protocol 076 Study Group*

Abstract Background and Methods. Maternal-infant transmission is the primary means by which young children become infected with human immunodeficiency virus type 1 (HIV). We conducted a randomized, double-blind, placebo-controlled trial of the efficacy and safety of zidovudine in reducing the risk of maternal-infant HIV transmission. HIV-infected pregnant women (14 to 34 weeks' gestation) with CD4+ T-lymphocyte counts above 200 cells per cubic millimeter who had not received antiretroviral therapy during the current pregnancy were enrolled. The zidovudine regimen included antepartum zidovudine (100 mg orally five times daily), intrapartum zidovudine (2 mg per kilogram of body weight given intravenously over a one-hour period, then 1 mg per kilogram per hour until delivery), and zidovudine for the newborn (2 mg per kilogram orally every six hours for six weeks). Infants with at least one positive HIV culture of peripheral-blood mononuclear cells were classified as HIV-infected.

Results. From April 1991 through December 20, 1993, the cutoff date for the first interim analysis of efficacy, 477 pregnant women were enrolled; during the study period, 400 gave birth to 415 live-born infants. HIV-infection status was known for 363 births (180 in the zidovudine group and 183 in the placebo group). Thirteen infants in the zidovudine group and 40 in the placebo group were HIV-infected. The proportions infected at 18 months, as estimated by the Kaplan-Meier method, were 8.3 percent (95 percent confidence interval, 3.9 to 12.8 percent) in the zidovudine group and 25.5 percent (95 percent confidence interval, 18.4 to 32.5 percent) in the placebo group. This corresponds to a 67.5 percent (95 percent confidence interval, 40.7 to 82.1 percent) relative reduction in the risk of HIV transmission (Z = 4.03, P = 0.00006). Minimal short-term toxic effects were observed. The level of hemoglobin at birth in the infants in the zidovudine group was significantly lower than that in the infants in the placebo group. By 12 weeks of age, hemoglobin values in the two groups were similar.

Conclusions. In pregnant women with mildly symptomatic HIV disease and no prior treatment with antiretroviral drugs during the pregnancy, a regimen consisting of zidovudine given antepartum and intrapartum to the mother and to the newborn for six weeks reduced the risk of maternal-infant HIV transmission by approximately two thirds. (N Engl J Med 1994;331:1173-80.)
PREP: Effectiveness of Studies

Effectiveness and Adherence in Trials of Oral and Topical Tenofovir-Based Prevention

Trials of oral and topical tenofovir-based PrEP show that these strategies reduce risk of HIV infection if they are used correctly and consistently. Higher adherence is directly linked to greater levels of protection.

Source: Salim S. Abdool Karim, CAPRISA
Future Challenges of HIV treatment

• State of the ART

• **Perfecting** ART

• Treatment as prevention

• Cure
Safety, Tolerability, Convenience: Newer Approaches

- **tenofovir alafenamide (TAF)**
  - TAF vs. TDF: Similar virologic efficacy
  - Switch TDF $\rightarrow$ TAF improved renal/bone markers

- **low dose EFV**
  - ENCORE 1 (TDF/FTC + [EFV 400 mg vs. 600 mg])

- **raltegravir 1200 mg QD**
Two Drug Regimens

• Nuc-lite and Nuc-sparing regimens
  • PI/r + 3TC (or FTC)
    • GARDEL (LPV/r): Cahn Lancet Infect Dis 2014;14:572
    • OLE (switch; LPV/r): Arribas Lancet Infect Dis 2015;15:785
    • SALT (switch; ATV/r): Perez-Molina Lancet Infect Dis 2015;15:775

• PI/r + integrase inhibitor
  • Second-Line (LPV/r + RAL) Boyd Lancet 2013;381:2091
  • NEAT-001 (DRV/r + RAL) Raffi Lancet 2014;384:1942
Two-drug Regimens

- **PADDLE Study**
  - Treatment-naïve individuals with HIV RNA 5-100K (N=20)
  - 2-drug regimen of DTG + 3TC
  - Results: All suppressed VL <50 by week 8→week 24
  - HIV RNA decline Sued CROI 2016 #947
    - -2.75 log cps/ml (PADDLE) vs. -2.5 (SPRING-1) and -2.6 (SINGLE)

→Friday 22nd – ROOM 6 – 13:00 _ 48 week PADDLE Results
The Future: all regimens as a single pill?

**NNRTI based**
- RPV/FTC/TDF
- EFV/FTC/TDF

**Integrase based**
- Elvitegravir/c/FTC/TDF
- DTG/ABC/3TC
- DTG/FTC/TAF
- DTG/FTC/TDF

**PI based**
- D/C/F/TAF

*and more to come...*
New Classes
BMS-663068: Oral HIV Attachment Inhibitor

• Prodrug of **BMS-626529**; inhibits CD4 binding to gp120
• Phase 1 (N=50)
  • ↓ baseline susceptibility in 12% of pts due to envelope polymorphisms

• Phase 2 (N=254) DeJesus CROI 2016 #472
  • Rx-experienced (≥1 wk on ≥1 ART); IC$_{50}$ <100 nM for BMS-529
  • TDF + RAL + [BMS-068 at 4 doses or ATV/r]
  • VL <50 (96 weeks): 61% (BMS-068) vs. 53% (ATV/r)
  • Adverse events leading to d/c (96 weeks): 2.5% (BMS-068) vs. 10% (ATV/r)

• Given FDA “Breakthrough Status” July 2015
• Phase 3: Rx-experienced subjects: in progress

Nettles JID 2012;206:1002
NRTTI - MK-8591 (EFdA)

- 4’-ethynyl-2-fluoro-2’-deoxyadenosine; EFdA
- Non-obligate chain terminator
- Inhibits RT by preventing translocation (NRTTI)
- Potent antiviral activity (PBMC EC50 = 0.2 nM) with broad coverage (HIV-1, HIV-2, MDR strains)
BMS-955176: Oral HIV Maturation Inhibitor

- Binds tightly to HIV GAG
- active in vitro against strains with polymorphisms and PI resistance
- Phase 1 (N=40)
  Hwang CROI 2015, #114LB

- Phase 2a (N=28)
  Hwang IAS 2015 #TUAB0106LB

- Phase 2b: in progress
On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection


ABSTRACT

BACKGROUND

Antiretroviral preexposure prophylaxis has been shown to reduce the risk of human immunodeficiency virus type 1 (HIV-1) infection in some studies, but conflicting results have been reported among studies, possibly due to challenges of adherence to a daily regimen.

METHODS

We conducted a double-blind, randomized trial of antiretroviral therapy for preexposure HIV-1 prophylaxis in men who have sex with men. Participants were randomly assigned to take a combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) or placebo before and after sexual activity. All participants received risk-reduction counseling and condoms and were regularly tested for HIV-1 and HIV-2 and other sexually transmitted infections.

RESULTS

Of the 414 participants who underwent randomization, 400 who did not have HIV infection were enrolled (199 in the TDF-FTC group and 201 in the placebo group). All participants were followed for a median of 9.3 months (interquartile range, 6.0 to 20.6). A total of 16 HIV-1 infections occurred during follow-up: 2 in the TDF-FTC group (incidence rate, 0.91 per 100 person-years) and 14 in the placebo group (incidence rate, 6.60 per 100 person-years), a relative reduction in the TDF-FTC group of 90% (95% confidence interval, 49 to 98; P = 0.002). Participants took a median of 15 pills of TDF-FTC or placebo per month (P = 0.57). The rates of serious adverse events were similar in the two study groups. In the TDF-FTC group, as compared with the placebo group, there were higher rates of gastrointestinal adverse events (14% vs. 5%, P = 0.002) and renal adverse events (18% vs. 10%, P = 0.03).

CONCLUSION

The use of TDF-FTC before and after sexual activity provided protection against HIV-1 infection in men who have sex with men. The treatment was associated with increased rates of gastrointestinal and renal adverse events. Funded by the National Institute of Allergy and Infectious Diseases (IANRS) and others: ClinicalTrials.gov number, NCT00743472.
<table>
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<tr>
<th>ARV</th>
<th>Mechanism</th>
<th>Dosing route</th>
<th>Dosing frequency</th>
<th>Current stage</th>
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<tr>
<td>Maraviroc</td>
<td>CCR5 antagonist</td>
<td>oral</td>
<td>once daily</td>
<td>Phase 2 enrolling</td>
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<td>Rilpivirine-LA</td>
<td>NNRTI</td>
<td>injectable, IM</td>
<td>once monthly</td>
<td>Phase 1 pilot; Phase 2 planned</td>
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<td>Dapivirine</td>
<td>NNRTI</td>
<td>ring</td>
<td>monthly</td>
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<td>injectable, IM</td>
<td>once quarterly</td>
<td>Phase 1 pilot; Phase 2 enrolling</td>
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Long-Acting Subdermal Implants: Tenofovir Alafenamide (TAF) in Dogs

Gunawardana, AAC 2015;59:3913
Injectable Drugs

• Rilpivirine (RPV) LA: Jackson Clin Pharmacol Ther 2014;96:314

• Cabotegravir (CAB): Spreen JAIDS 2014;67:481

LATTE-2: Cabotegravir IM + Rilpivirine IM for Long-Acting Maintenance ART

- Multicenter, open-label phase IIb study
  - Primary endpoints: HIV-1 RNA < 50 c/mL by FDA snapshot, PDVF, and safety at maintenance Wk 32

Induction Phase*  
CAB 30 mg PO QD + ABC/3TC

Maintenance Phase
CAB 400 mg IM + RPV 600 mg IM Q4W (n = 115)
CAB 600 mg IM + RPV 900 mg IM Q8W (n = 115)
CAB 30 mg PO + ABC/3TC PO QD (n = 56)

*Pts with HIV-1 RNA < 50 c/mL from Wk 16 to Wk 20 continued to maintenance phase. 6 pts discontinued for AEs or death in induction analysis.


Slide credit: clinicaloptions.com
LATTE-2: Maintenance Wk 32 Virologic Efficacy (ITT-Maintenance Exposed)

- Virologic efficacy of Q4W and Q8W IM regimens similar to oral regimen
- No INSTI, NNRTI, or NRTI resistance mutations detected


Slide credit: clinicaloptions.com
LATTE-2: Maintenance Wk 32 Virologic Efficacy (ITT-Maintenance Exposed)

- Virologic efficacy of Q4W and Q8W IM regimens similar to oral regimen.
- No INSTI, NNRTI, or NRTI resistance mutations detected.


Slide credit: clinicaloptions.com
Future of ART

• Antiretroviral Therapy
  • Active
  • Safe and tolerable
  • Convenient
  • Affordable
  • Accessible
  • Life expectancy

↔ (↑ for MDR)

↑

↑

↑

↑↑

WHO Goal: “20 by 20” same (better?) than general population
Antiretroviral Therapy: The Future

- HIV-1 discovered
- ZDV monotherapy
- ZDV/3TC
- Triple Drug Therapy
- Single Tablet Regimens
- Integrase Era
- Long Acting Injectable?


Slide courtesy of Joe Eron, MD
Future Challenges of HIV treatment

- State of the ART
- Perfecting ART
- Treatment as prevention
- Cure
World AIDS Conference
DURBAN, 2000
2015 an amazing target achieved

Number of people receiving antiretroviral therapy, 2000–2015
MAKE END AIDS by 2030
GOAL NO. 1 IN POST 2015 DEVELOPMENT AGENDA
Is it reachable?
90 90 90: THE UNAIDS STRATEGY TO FURTHER CURB THE HIV EPIDEMIC
based on expanded access to treatment and on the “treatment as prevention” concept

90% of all people living with HIV will know their HIV status.

90% of all people diagnosed with HIV will receive sustained antiretroviral therapy.

90% of all people receiving antiretroviral therapy will have durable suppression.
“The AIDS response is at a crucial juncture, both in its immediate trajectory and its sustainability…”

Number of new HIV Infections in LMICs (millions)

- Ambitious Fast-Track targets
- Maintaining 2013 levels of coverage

Source: Adapted from UNAIDS Fast-track Report
A reality check...
1st 90 – 90% diagnosis for Full cascades

Percentage of Total HIV Positive People Receiving Diagnosis for 31 Countries with Full Cascades

UNAIDS 90-90-90 Target of 90% Diagnosed
2\textsuperscript{nd} 90 – 81\% on ART for 31 Full cascades

Percentage of Total HIV Positive People Receiving ART
for 31 countries with Full cascades

UNAIDS 90-90-90
Target of 81\% on ART
3rd 90 – 73% achieving viral suppression for 31 Full cascades

Percentage of Total HIV Positive People
Achieving Undetectable HIV RNA For 31 Countries with Full Cascades

UNAIDS 90-90-90 Target of
73% Viral Suppression
New HIV infections among adults (aged 15 years and older), global, 2000–2015

Source: UNAIDS 2016 estimates.
GENEVA, 12 July 2016—A new report by UNAIDS reveals concerning trends in new HIV infections among adults. The *Prevention gap report* shows that while significant progress is being made in stopping new HIV infections among children (new HIV infections have declined by more than 70% among children since 2001 and are continuing to decline), the decline in new HIV infections among adults has stalled. The report shows that HIV prevention urgently needs to be scaled up among this age group.
Five pillars for achieving less than 500 000 new infections by 2020

Getting back on track to reducing new infections to 500 000 by 2020 requires continued progress towards the 90–90–90 target and intensive focus on five prevention pillars delivered through a people-centred, combination approach:

1. Combination prevention, including comprehensive sexuality education, economic empowerment and access to sexual and reproductive health services for **young women and adolescent girls and their male partners** in high-prevalence locations.

2. Evidence-informed and human rights-based prevention programmes for **key populations**, including dedicated services and community mobilization and empowerment.

3. Strengthened national **condom programmes**, including procurement, distribution, social marketing, private-sector sales and demand creation.

4. **Voluntary medical male circumcision** in priority countries that have high levels of HIV prevalence and low levels of male circumcision, as part of wider sexual and reproductive health service provision for boys and men.

5. **Pre-exposure prophylaxis** for population groups at higher risk of HIV infection.
Diversity of HIV epidemics: interventions shall be targeted

Figure 4: The importance of location and population
Source: The Gap Report.4

People living with HIV (children and adults) are included as members of all of the featured populations. They are implicitly included in this map as they must have universal access to services.
High rates of HIV among key populations: young women in Africa


Young women have up to 8 times more HIV than men

Source: Adapted from UNAIDS 2012

HIV prevalence in young pregnant women in rural Vulindlela, South Africa (2005-2008)

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>HIV Prevalence (N=1237)</th>
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<tr>
<td>≤16</td>
<td>10.6%</td>
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<tr>
<td>17-18</td>
<td>21.3%</td>
</tr>
<tr>
<td>19-20</td>
<td>33.0%</td>
</tr>
<tr>
<td>21-22</td>
<td>44.3%</td>
</tr>
<tr>
<td>23-24</td>
<td>51.1%</td>
</tr>
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</table>

EXPLOITED YOUNG WOMEN
Key populations at high risk of acquiring HIV

- Injecting drug users: 36x
- Transgender women: 21-49x
- Men who have sex with men: 17x
- Female sex workers: 10x
- Prevalence of HIV among inmates: 6x
- Migrants

New infections among key populations, 2014

- Sex workers: 4%
- People who inject drugs: 7%
- Men who have sex with men: 8%
- Transgender people*: 0.4%
- Clients and other sex partners: 16%
- Rest of population: 65%

* Reflects only Asia and Pacific and Latin America regions
Starting patients on ART is just the first step....

.....retaining people in therapy and keep the virus fully suppressed (for years) is far more complicated....
Retention in ART

Global analysis of retention in care in initial HIV care and treatment program in the IeDEA regions (41 countries)

WHO-IeDEA collaboration, 2015
SIMPLIFY THE WAY I GET ARVs.
I AM TIRED OF WALKING.
The new ART eligibility criteria will increase the proportion of asymptomatic patients in ART programs. As they are still well, these patients may perceive no short-term benefit from entering treatment, with consequent ART cessation, especially in the face of onerous ART procurement or regimens with persistent side effects.

“Why shall I take this pill every day if I am feeling well”

“Yes, I stopped my medication because I feel better and think I am cured”
AN OVERARCHING BARRIER: WHO WILL PAY?

<table>
<thead>
<tr>
<th>Key parameters</th>
<th>2005</th>
<th>2015</th>
<th>2020</th>
<th>2030</th>
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<tbody>
<tr>
<td>New HIV infections</td>
<td>3 million</td>
<td>2 million</td>
<td>500,000</td>
<td>200,000</td>
</tr>
<tr>
<td>AIDS-associated deaths</td>
<td>2.4 million</td>
<td>1.2 million</td>
<td>500,000</td>
<td>400,000</td>
</tr>
<tr>
<td>PLHIV accessing ART</td>
<td>1.5 million</td>
<td>15 million</td>
<td>30 million</td>
<td>ALL</td>
</tr>
<tr>
<td>Investments for global HIV response (US$)</td>
<td>7 billion</td>
<td>20 billion</td>
<td>32 billion</td>
<td>29 billion</td>
</tr>
</tbody>
</table>

WHO & UNAIDS reports, 2014 & 2015
“Science, innovation and research have provided new and effective HIV prevention options, rapid diagnostics and improved treatment for HIV,” said Mr Sidibé. “Investing in innovation is the only way to secure the next big breakthrough—a cure or a vaccine.”
Huge progress has been made so far to curb the AIDS epidemic.

A mistake would be to consider this as the “beginning of the end”.

We probably are just at the “end of the beginning”.

In July 1996, researchers, policymakers, and activists involved in the fight against HIV/AIDS met in Vancouver, Canada, for the 11th International Conference on AIDS. During that historic meeting, practitioners and patients heard evidence regarding a powerful weapon to stop the relentless onslaught of the human immunodeficiency virus (HIV): combination antiretroviral therapy (ART), with a protease inhibitor as the centerpiece of the regimen. In the nearly 20 years since that watershed meeting, the early promise of durable effects from combination therapy has been realized for many patients: between 2000 and 2014, the rollout of ART saved an estimated 7.8 million lives worldwide.

Despite this success, the timing of ART initiation has remained the subject of intense debate. As with any therapy, clinicians and their patients weighed ART’s benefits against its risks, and the results of that calculus seemed to depend on the patient’s stage of illness. Specifically, evidence supporting treatment later in the course of HIV infection, when the CD4+ T-cell count fell below a certain critical level, seemed far stronger than that supporting early treatment (particularly given the toxic effects associated with the first approved antiretroviral drug). Today, a series of well-designed efficacy studies conducted over a period of more than a decade has fundamentally changed this discussion.

In addition, researchers continue to accrue promising data on the concept of using ART for HIV prevention in HIV-negative persons — preexposure prophylaxis (PrEP). Findings from the landmark Intervention Preventive de l’Exposition aux Risques avec et pour les Gays (IPERGAY) study, now reported in the Journal (pages 2227–2246), demonstrate the safety and efficacy of “on-demand” PrEP for men who have sex with men and transgender women (persons who are born male but identify as female), who are at high risk for HIV infection. In this study, persons who took PrEP in an event-driven manner around the time of sexual activity were 48% less likely to acquire HIV infection than those taking placebo.

Taken together, these studies have shown definitively that the benefits of prompt initiation of ART — regardless of the CD4+ T-cell count — outweigh the risks, for both the infected person and uninfected sexual partners and that PrEP can be implemented in a way that is both acceptable to patients and safe and effective in blocking HIV transmission. With regard to ART initiation, three critical questions were asked and answered by a “trifecta” of large international randomized, controlled trials over the course of a decade:

- Combination Prevention
- Perfecting ART
- HIV Vaccine
- HIV Cure
Note: PMTCT, Screening transfusions, Universal precautions, etc. have not been included.
HIV CURE
Why do we need a cure for HIV infection

• The HIV/AIDS pandemic represents the most important global health challenge in modern history.
• Fortunately, when used optimally, combination antiretroviral therapy (ART) can effectively control HIV replication, prevent the development of AIDS, prolong life and reduce the risk of transmission.
• Despite this unquestionable success, the current treatment strategies have limitations.
• The operational and logistical challenges involved in delivering lifelong treatment are daunting, and the economic costs of providing ART to the more than 35 million people who are currently living with HIV might be unsustainable.
Toward an HIV Cure: Why do we need novel therapeutic strategies?

- **Treatment = Prevention of HIV infection**
- **37 millions PLWH: 16 millions on cART**
  - Only 41% of the people eligible under new WHO 2015 guidelines
  - Too few countries with >80% coverage
- **Lifelong cART:**
  - Substantial stigma and discrimination
  - Difficult adherence
  - Life expectancy still reduced with non AIDS-related morbidity
  - Long term-cost *(approximately US$ 30 billion required in 2030)* with limited investments of low-and middle income countries

Lifelong ART for all is unlikely to be sustainable...

Patients hopes and willingness!

F. Barrè Sinoussi
Definition of cure...

• The optimal outcome would be the **complete eradication** within an individual of all replication-competent HIV. Such a sterilizing cure will be challenging to achieve and impossible to prove with current technologies.

• A more feasible outcome will be the achievement of **long-term remission**. Remission is likely to be a necessary precursor for the development of an HIV cure, and is increasingly utilized in the field to indicate the goal of long-term undetectable viremia for an as-yet-undefined period (probably of several years) in the absence of ART.
# HIV cure

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<th>Eradication</th>
<th>Remission</th>
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Sustained remission off ART is rare but achievable

### HIV cure

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Barriers to an HIV cure

HIV persistence in tissues

Latently infected cells are rare and undistinguishable from uninfected cells

Latently infected cells are diverse

Eradication strategy should reach tissues

Eradication strategy should be specific

Eradication strategy should target all infected cells

N. Chomont, IAS 2015
Future HIV Cure Strategies?
A combined affordable and scalable approach...

Gene therapy
To make cells resistant to HIV and/or to excise latent HIV To make genetic engineering of T cells

Early Treatment optimization
To limit reservoirs and control viral replication

Latency Reversing Agents (LRA)
to activate/definitively repress latent HIV

Immune-based Therapies (inspired from cancer therapy)

Cure? Remission off ART?

Discovery of Novel Biomarkers Predictive of Remission?
Personalized/Individualized cure therapy?

F. Barrè Sinoussi
Precisely remove the entire HIV-1 genome spanning between 5’ and 3’ LTRs of integrated HIV-1 proviral DNA copies from latently infected human CD4+ T-cells.
Future HIV Cure Strategies?
A combined affordable and scalable approach...

**Gene therapy**
To make cells resistant to HIV and/or to excise latent HIV
To make genetic engineering of T cells

**Early Treatment optimization**
To limit reservoirs and control viral replication

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to activate/definitively repress latent HIV

**Therapeutic vaccination**
To enhance host innate and adaptive B and T cells immune responses

**Immune-based Therapies (inspired from cancer therapy)**

Cure? Remission off ART?

Discovery of Novel Biomarkers Predictive of Remission?

F. Barrè Sinoussi
MAY BE THE MAJOR OBSTACLE...

Box 4 Measuring HIV persistence in virally suppressed individuals

The estimated number of cells infected with HIV that persist on ART differs depending on the methodology used. Approximately 100–1,000 CD4⁺ T cells per million cells contain HIV genomes (HIV DNA). Only a fraction of these cells make cell-associated (CA) HIV RNA, and a smaller fraction have detectable HIV proteins or release virions into supernatant. A smaller fraction of cells generates replication-competent HIV in vitro after stimulation by T cell receptor (TCR) ligation (green circle; ~1/106 cells). However, sequencing of viral genomes indicates that the 'real' size of the reservoir (intact genomes, brown oval; ~60/106 cells) might be much larger than this.
Future HIV Cure Strategies?  
A combined affordable and scalable approach...

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Cure?  
Remission off ART?

Discovery of Novel Biomarkers Predictive of Remission?

F. Barrè Sinoussi
Title of Proposal:
European HIV Vaccine Alliance (EHVA): an EU platform for the discovery and evaluation of novel prophylactic and therapeutic vaccine candidates

List of participants:

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<tr>
<th>Part. No</th>
<th>Participant Organization Name</th>
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This project has received funding from the European Union’s horizon 2020 research and innovation programme under grant agreement No 681032.
Promote viral expression from latency and knock off expressing cells

The shock and kill strategy:

– can we shock enough safely?
  → only a few “encouraging” papers

– do we have or can we generate enough well armed “defenders” to reach and kill enough expressing targets?
  → working on HIV-specific immune response
Regulation of CD8+ T cells after acute/chronic viral infection. Highly complex network of co-inhibitory and co-stimulatory signaling pathways regulate the outcome of virus-specific CD8 T cells. High amount of antigen drives the exhaustion of virus-specific CD8+ T cells during chronic viral infection that is evidenced by the expression of multiple immune-inhibitory receptors. (Note: Exhausted T cells with loss of function may not control chronic viral infection). However, during acute viral infection the antigen is cleared from the host and the virus-specific CD8 T cells are fully functional and produce cytokines and have proliferative potential, survival and cytotoxicity to control viral infection.

Download authors' original image
**Figure 2.**

PD-1 blockade enhances both T and B cell responses during chronic HIV/SIV infection. PD-1 blockade mediated functional restoration of exhausted virus-specific CD8⁺ T cells gain their qualities to clear viral antigens and control chronic viral infection. Blockade of PD-1 in virus specific CD4⁺ T cells restore functions associated with CD8⁺ T cell help and B-cell activation. Impaired B cells restore functions and produce virus-specific antibody following in vivo PD-1 blockade.


*Download authors' original image*
Activated T cells up-regulate immune checkpoint molecules such as CTLA-4 and PD-1, which act to abrogate T cell responses.

Antibody blockade of immune checkpoints enhances T cell responses.

Activated T cells make IFN-γ which increases PD-L1 expression.

PD-1
CTLA-4

Immune checkpoint therapy

anti-PD-1
anti-CTLA-4

Tumor cell

Biopsy at this time would show PD-L1-negative cells

Enhanced T cell infiltration into tumor tissue

Biopsy at this time would show PD-L1-positive cells
Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

Nivolumab in Previously Untreated Melanoma without BRAF Mutation

Overall Survival

Duration of Response
Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer


ABSTRACT

BACKGROUND
Programmed death 1 (PD-1) protein, a T-cell coinhibitory molecule, and its ligand PD-L1, play a pivotal role in the ability of tumor cells to evade the immune system. Blockade of interactions between PD-1 and PD-L1 in vitro and mediates antitumor activity in preclinical models.

METHODS

We assessed the efficacy and safety of programmed cell death 1 (PD-1) inhibition with pembrolizumab in patients with advanced non–small-cell lung cancer enrolled in a phase 1 study. We also sought to define and validate an expression level of the PD-1 ligand 1 (PD-L1) threshold associated with the likelihood of clinical benefit.
Immune check-point mediated T-cell Exhaustion
Anti-PD-1

Anti-LAG3

↑ activation/proliferation
Combined LAG-3 and PD-1 signaling blockade enhances proliferation as compared to PD-1 signaling blockade alone in virus specific CD8 T cells.

Combined anti-LAG-3 and anti-PD-1 antibody treatment shows the greatest potential for enhanced proliferative effect of HIV CD8 T cells compared to PD-1 blockade alone.
Thanks to....

- Charles Boucher
- Anton Pozniak
- Trip Gulick
- Francoise Barrè-Sinoussi
- Raffaella Bucciardini
- my Mab group...