Best of en Infectiologie
Infection par le VIH/SIDA

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Déclaration d’intérêts de 2012 à 2015

- Bourse de Recherche: Gilead Sciences, Merck
- Advisory Boards: Gilead Sciences, Merck, ViiV, BMS, Janssen
Timing of Antiretroviral Treatment During Pregnancy in 8075 Women

<table>
<thead>
<tr>
<th>Children Status</th>
<th>All Children No. (PT %)</th>
<th>Before Conception No. (PT %)</th>
<th>1st Trimester (&lt; 14 GW) No. (PT %)</th>
<th>2nd Trimester (14-27 GW) No. (PT %)</th>
<th>3rd Trimester (&gt; 27 GW) No. (PT %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-infected</td>
<td>56 (0.7)</td>
<td>10 (0.2)</td>
<td>3 (0.4)</td>
<td>22 (0.8)</td>
<td>21 (2.1)*</td>
</tr>
<tr>
<td>Not Infected</td>
<td>8019 (92.4)</td>
<td>3798 (92.8)</td>
<td>655 (91.9)</td>
<td>2597 (92.7)</td>
<td>969 (90.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>486 (5.6)</td>
<td>227 (5.5)</td>
<td>45 (6.3)</td>
<td>144 (5.1)</td>
<td>70 (6.5)</td>
</tr>
</tbody>
</table>

*P value < 0.001
Perinatal HIV Transmission Rate According to Timing of ART Initiation and Maternal Viral Load at Delivery

<table>
<thead>
<tr>
<th>Maternal Plasma HIV RNA Level at Delivery</th>
<th>Before Conception</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Trimester (&lt; 14 GW)</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Trimester (14-27 GW)</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; Trimester (&gt; 27 GW)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.PT/Total</td>
<td>PT% (95% CI)</td>
<td>No.PT/Total</td>
<td>PT% (95% CI)</td>
</tr>
<tr>
<td>&gt; 400</td>
<td>5/230</td>
<td>2.2 (0.7-5)</td>
<td>1/69</td>
<td>1.5 (0.4-7.8)</td>
</tr>
<tr>
<td></td>
<td>10/228</td>
<td>4.4 (2.1-7.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-400</td>
<td>1/301</td>
<td>0.3 (.01-1.8)</td>
<td>1/61</td>
<td>1.6 (0.4-8.8)</td>
</tr>
<tr>
<td></td>
<td>9/297</td>
<td>3.0 (1.4-5.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>0/2651</td>
<td>0.0 (0-0.1)*</td>
<td>1/507</td>
<td>0.2 (.01-1.1)</td>
</tr>
<tr>
<td></td>
<td>4/452</td>
<td>0.9 (0.2-2.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* P value = 0.002

Elimination of Perinatal HIV transmission can be achieved in pregnant women who are tested for HIV, start ART before conception and maintain suppression of plasma VL.

Mandelbrot et al, CID 2015
Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial


HIV-negative Gay Men and transgender women reporting unprotected anal intercourse with a man in previous 90 days

- **Primary endpoint**: Time to accrual of 500 participants and retention
- **From June 2014**: HIV-infection in first 12 months
- **Other outcome measures**: safety, adherence, risk compensation
- All participants were offered a risk reduction package: regular HIV testing, diagnosis and treatment of STIs, support to reduce high risk behavior including condoms, PEP.

Immediate Daily Oral TDT/FTC
(n = 275)

Deferred Daily TDF/FTC by 12 months
(n = 269)
### Incidence of HIV-Infection

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of infections</th>
<th>Follow-up (PY)</th>
<th>Incidence (per 100 PY)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>23</td>
<td>465</td>
<td>5.0</td>
<td>3.5–6.9</td>
</tr>
<tr>
<td>Immediate</td>
<td>3</td>
<td>243</td>
<td>1.2</td>
<td>0.4–2.9</td>
</tr>
<tr>
<td>Deferred</td>
<td>20</td>
<td>222</td>
<td>9.0</td>
<td>6.1–12.8</td>
</tr>
</tbody>
</table>

**Efficacy** = 86% (90% CI: 64-96%)  
P-value = 0.0001

**Number Needed to Treat** = 13 (90% CI: 9 – 23)

**PEP use**: 85 individuals (32%) in the deferred arm with 5 infections

S. McCormack et al Lancet 2015
## Bacterial Sexually Transmitted Infections

<table>
<thead>
<tr>
<th></th>
<th>Immediate</th>
<th>Deferred</th>
<th>Unadjusted OR</th>
<th>Adjusted* OR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>152/265 (57%)</td>
<td>124/247 (50%)</td>
<td>1.33</td>
<td>1.07</td>
<td>0.74</td>
</tr>
<tr>
<td>Gonorrhoea</td>
<td>103/261 (39%)</td>
<td>89/242 (37%)</td>
<td>1.12</td>
<td>0.86</td>
<td>0.46</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>77/261 (30%)</td>
<td>54/242 (22%)</td>
<td>1.46</td>
<td>1.27</td>
<td>0.27</td>
</tr>
<tr>
<td>Syphilis</td>
<td>30/263 (11%)</td>
<td>22/247 (9%)</td>
<td>1.32</td>
<td>1.29</td>
<td>0.39</td>
</tr>
<tr>
<td>Rectal Infection</td>
<td>93/258 (36%)</td>
<td>77/238 (32%)</td>
<td>1.18</td>
<td>1.00</td>
<td>0.99</td>
</tr>
</tbody>
</table>

*Adjusted for the number of screens for specific infections

S. McCormack et al Lancet 2015
On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection

Double-Blinded Randomized Placebo-Controlled Trial

- 400 HIV negative MSM
- Condomless anal sex with > 2 partners within 6 m
- eGFR > 60 mL/mn

Full prevention services*
TDF/FTC before and after sex

Full prevention services*
Placebo before and after sex

* Counseling, condoms and gels, testing and treatment for STIs, vaccination for HBV and HAV, PEP

- Follow-up visits: month 1, 2 and every two months thereafter with 4th generation HIV ELISA assays (combined Ab/Ag detection) on serum

Molina JM et al. NEJM 2015
Mean follow-up of 13 months: 16 subjects infected

14 in placebo arm (incidence: 6.6 /100 PY) and 2 in TDF/FTC arm (0.91 /100PY)

86% relative reduction in the incidence of HIV-1 (95% CI : 40-98, p=0.002)

Molina et al NEJM 2015
## Adverse Events

<table>
<thead>
<tr>
<th>Nb of Participants (%)</th>
<th>TDF/FTC n=199</th>
<th>Placebo n=201</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Serious AE</td>
<td>20 (10)</td>
<td>17 (8)</td>
<td>0.58</td>
</tr>
<tr>
<td>Any Grade 3 or 4 AE</td>
<td>19 (10)</td>
<td>15 (7)</td>
<td>0.45</td>
</tr>
<tr>
<td>Treatment D/C due to AE</td>
<td>1* (&lt;1)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Drug-Related GI AEs</td>
<td>28 (14)</td>
<td>10 (5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>16</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Elevated Creatinine</td>
<td>35 (18)</td>
<td>20 (10)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* deep veinous thrombosis with suspected DDI with dabigatran

Molina JM et al. NEJM 2015
• 49 women received a single-dose of TDF (150 to 600 mg) or FTC (100 to 400 mg) with blood and rectal, cervical, and vaginal sampling over 48h.

• PK/PD model using tissue concentrations of TFV, FTC, TFV-DP and FTC-TP and competing endogenous nucleotides.

• Cell line (TZM-bl) and CD4 T-cells used to identify 90% Effective Concentration (EC$_{90}$) ratios of TVF-DP to dATP and FTC-TP to dCTP.

• Percentage of the simulated population achieving the EC$_{90}$ ratio for TDF or TDF/FTC over 14 days following a single coitus in colorectal tissue with the first dose given 24h (A) or 2 h (B) before coitus.

• TDF+FTC achieved target exposure at the time of coitus in 81% (A) and 98% (B) of the population, and was sustained for 240h (10 days) after coitus.
All adults evaluated for PrEP from July 2012 through Feb 2015
- Patients surveyed by email about changes in sexual behavior.
- Among 801 individuals with at least one visit, 657 (82%) started PrEP.
- Mean duration of PrEP use: 7.2 months.
- Mean age was 37 years, 99% were MSM, 84% report multiple sex partners
- 187 (28%) were diagnosed with at least one STI during FU
- No HIV diagnoses during follow-up (97.5% CI: 0-1%)
- Nb sexual partners unchanged in 74%, decreased in 15%, increased in 11%
- Condom use unchanged in 56%, decreased in 41% and increased in 3%
- How changes in sexual behavior may impact the risk for STIs in PrEP users.
Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women

- **ASPIRE Trial** *(A Study to Prevent Infection with a Ring for Extended use)*
  Phase 3 multicentric, randomized (1:1), double blinded, placebo controlled study of a vaginal ring containing Dapivirine for HIV prevention in women

- **Methods**
  - Vaginal ring inserted every month at each monthly visit
  - “Counseling” for HIV prevention at each visit with free condoms
  - Women were tested monthly for pregnancy

- **Participants Characteristics**
  - 2,629 women enrolled from 2012 to 2015 in Africa (Malawi, South Africa, Uganda and Zimbabwe)
  - Median age: 26 years, 41% married, and 17% > 1 partner in past 3 months
  - Partner aware of ring use: 64%
  - 57% reported condom use at last vaginal intercourse

In women randomized in the dapivirine ring arm the relative reduction of HIV incidence was 27% (95% CI: 1 to 46).

Cumulative Incidence of HIV-1 Infection According to Age at Enrollment

| Age: 18-21 years | 18 - 21 years | HIV Incidence per year in placebo arm | 5.4 % |
| Age: 22-26 years | 22 - 26 years | Relative Efficacy of Dapivirine ring | - 27 % (- 133 - 31) |
| Age: 27-45 years | 27 - 45 years | | 56 % (19 - 76) |

- No protection of Dapivirine ring in women ≤ 21 years vs. 56% in those > 21 years
- This difference was correlated with reduced adherence as assessed by dapivirine plasma levels

Prospective Study of Acute HIV-1 Infection in Adults in East Africa and Thailand


- RV 217 study: Prospective study in 2276 volunteers at high risk of HIV-infection in Sub-Saharan Africa and Thailand (twice weekly visits)

- 50 of 112 pts with acute HIV-infection had samples collected before HIV-1 Ab detected
  - Median peak viremia: 13 days after first sample positive on RNA testing
  - Nadir viremia at 31 days and equivalent to the viral load set point
  - EIA reactivity after a median of 14 days

- Clinical symptoms rare:
  - 50% reported neither symptoms nor signs
  - Just before and at the time of peak viremia

- High level of HIV RNA in asymptomatic patients with acute infection and no detectable HIV antibodies may limit the effect of test and treat strategies on HIV transmission
617 infections in MSM: 71% of transmissions from undiagnosed men, 6% from men on ART

Annual Testing + Immediate ART + PrEP could prevent up to 66% of HIV infections

2375 MSM enrolled in the multicenter AIDS cohort study from 1994 to 2003 with no HBV infection.

- Median follow-up: 9.5 years with 244 HBV infections: incidence rate of 9.6 per 1000 PYs (100 fold higher than in the general population).

- Effective ART was associated with reduced rates of incident HBV infection

- 6 of 262 men receiving ART regimens with an HBV-active drug (3TC/FTC or TDF) who had an HIV RNA level < 400 cp/ml developed HBV infection, with an incidence rate of 2.6 per 1000 PYs

- Receiving ≥1 dose of the HBV vaccine decreased the risk of HBV infection by 70%

- There is an urgent need for HBV vaccination in MSM

Receiving >1 dose of the HBV vaccine decreased the risk of HBV infection by 70%

Randomized, non-inferiority, multicenter trial (OPTION - ACTG A5241)
- Primary endpoint: regimen failure (VF or discontinue NRTI assignment)

Stratified by choice of maraviroc, enfuvirtide, integrase inhibitor and NRTIs susceptibility score

Treatment-experienced pts failing on PI-based regimen with NRTI, NNRTI experience and/or resistance
- VL > 1,000 cp/ml
- No HBV-infection
- (N = 360)

48 weeks Primary Endpoint
96 weeks Secondary Endpoint

Omit-NRTIs Optimized Regimen* (n = 179)

Add-NRTIs Optimized Regimen* (n = 181)

*choice based on treatment history, prior intolerance and genotypic and phenotypic viral resistance tests to construct a salvage regimen with a phenotypic susceptibility score > 2.

Primary Outcome of Regimen Failure and Its Components

- Most common salvage ARV regimen used: DRV/r + raltegravir + either etravirine or maraviroc (86%) and most common NRTIs used: TDF+ FTC or 3TC (81%)
- Similar virologic suppression (HIV-1 RNA < 50 c/mL) in each arm (~ 65%) and similar CD4+ cell count increases in each arm (90-106 cells/mm³)
- No significant difference in any safety outcome when globally evaluating symptoms and laboratory abnormalities, however:
  - Significant increase in non-HDL cholesterol in the omit-NRTIs arm
  - However, more deaths in add-NRTIs arm

Safety and efficacy of the HIV-1 attachment inhibitor prodrug BMS-663068 in treatment-experienced individuals: 24 week results of AI438011, a phase 2b, randomised controlled trial

Jacob P Lalezari, Gulam H Latiff, Cynthia Brinson, Juan Echevarria, Sandra Treviño-Pérez, Johannes R Bogner, Melanie Thompson, Jan Fourie, Otto A Sussmann Pena, Fernando C Mendo Urbina, Marcelo Martins, Iulian G Diaconescu, David A Stock, Samit R Joshi, George J Hanna, Max Lataillade, for the AI438011 study team

- Randomized, open-label, 96-week, Phase 2b study
  - Primary endpoints: proportion of patients with an HIV-1 RNA <50 cp/ml at week 24 and frequency of SAEs and AEs leading to discontinuation

Stratified by baseline AI IC_{50}
(25% not assessable - 6% not susceptible)

Treatment-experienced pts failing on 1st or 2nd line ART
  - VL > 1,000 cp/ml
  - > 50 CD4
  - No TDF, ATV or RAL resistance
  - AI IC_{50} < 100 nmol/L
(N = 254)

BMS-66068 400 to 1200 mg
TDF + Raltegravir
(n = 203)

Atazanavir/ritonavir
TDF + Raltegravir
(n = 51)
Antiviral Activity of the HIV-1 Attachment Inhibitor in Treatment-Experienced Patients

### Table: Treatment Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number (mg)</th>
<th>Dose</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS-663068 + TDF + RAL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 mg BID</td>
<td>50</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td>800 mg BID</td>
<td>49</td>
<td>800</td>
<td></td>
</tr>
<tr>
<td>600 mg QD</td>
<td>51</td>
<td>600</td>
<td></td>
</tr>
<tr>
<td>1200 mg QD</td>
<td>50</td>
<td>1200</td>
<td></td>
</tr>
<tr>
<td>ATV/r + TDF + RAL</td>
<td></td>
<td></td>
<td>n = 51</td>
</tr>
</tbody>
</table>

### Key Findings:

- No patients who met criteria for resistance testing in the ATV/R developed drug resistance.
- 40% of patients (8/19) who failed in the AI arm had virus with a 3-fold increase in IC$_{50}$ from baseline and 4/8 also developed raltegravir resistance.

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**Figure 2:** Median change in HIV-1 RNA viral load from baseline for patients participating in the BMS-663068 monotherapy substudy.
Empirical tuberculosis therapy versus isoniazid in adult outpatients with advanced HIV initiating antiretroviral therapy (REMEMBER): a multicountry open-label randomised controlled trial

Mina C Hosseinipour*, Gregory P Bisson*, Sachiko Miyahara, Xin Sun, Agnes Moses, Cynthia Riviere, Fredrick K Kirui, Sharlaa Badal-Faesen, David Lagat, Mulinda Nyirenda, Kogielem Naidoo, James Hakim, Peter Mugenyi, German Henostroza, Paul D Leger, Javier R Lama, Lerato Mohapi, Jorge Alave, Vidya Mave, Valdilea G Veloso, Sandy Pillay, Nagalingeswaran Kumarasamy, Jing Bao, Evelyn Hogg, Lynne Jones, Andrew Zolopa, Johnstone Kumbwenda, Amita Gupta, for the Adult AIDS Clinical Trials Group A5274 (REMEMBER) Study Team†

Stratified by CD4 counts (> or < 25) and prognosis factors (BMI, anemia, hospital admission)

Treatment-naive pts
TB excluded
(symptoms screen, chest X-ray, sputum smears using GeneXpert and cultures)
CD4 < 50 cells/mm³
ALT < 2.5 ULN
(N = 850)

Primary endpoint: survival (death or unknown status)
Study powered to detect a 7.5% difference in death rate

24 weeks Primary Endpoint
96 weeks End of Follow-up

TB treatment + EFV-containing ART (n = 424)

INH Therapy + EFV-containing ART (n = 426)

Cumulative Probability of Time to Death or Probable or confirmed TB

- At week 24, 5% of participants from each group died or were of unknown status: absolute risk difference of -0.06% (95% CI -3.05 to 2.94).
- Higher rate of TB in the empirical arm (31 vs 18 in the INH group) with more Rx discontinuations (11% vs 4%)
- Grade 3 or 4 signs or symptoms occurred in 12% in the empirical group and 11% in the INH arm.
- Grade 3 or 4 lab abnormalities occurred in 23% of participants in both arms.
- TB drug resistance in 3 patients per arm
- No benefit in rate of bacterial infections (9% vs 12%, p = 0.095)