Care of HIV-2 positive individuals in Europe

European Guidelines
HIV2EU Expert Group

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The HIV-2 world – a world of estimates

Prevalence (1-5%):
- Guinea-Bissau
- Senegal
- The Gambia
- Sierra Leone
- Ivory Coast

Moderate prevalence (<1%) in all other West African countries, including Cape Verde

Guinea-Bissau (population 1 800 000) HIV-2
~90 000-18 000

Incidence HIV-2 decreasing (8.3% - 4.7%)
Incidence HIV-1 increasing (0.5%-3.6%)
# HIV-2 in Europe

Europe:

<table>
<thead>
<tr>
<th>Country</th>
<th>Number</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>1091</td>
<td>1.8% of new reported HIV infections (-6,500) are due to HIV-2 (120)</td>
</tr>
<tr>
<td>Portugal</td>
<td>1813</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>338</td>
<td></td>
</tr>
<tr>
<td>Germany (RKI)</td>
<td>~100</td>
<td>(HIV-1: 77,500)</td>
</tr>
<tr>
<td>reported new in 2016</td>
<td>13</td>
<td>(HIV-1: 3,100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dual Infections: 5</td>
</tr>
</tbody>
</table>

The rationale for guidelines in Europe: HIV-2 is rare, *but different*...
HIV-2 EU expert group: Guidelines „Care of HIV-2 positive individuals in Europe“

HIV-2 EU expert group:
2018:
Guidelines for the care of HIV-2 positive individuals in Europe:
- diagnostics
- treatment start
- first line treatment (active agents)
- second line treatment & resistance

2013
HIV-2EU: Supporting Standardized HIV-2 Drug Resistance Interpretation in Europe

2015
HIV-2EU—Supporting Standardized HIV-2 Drug-Resistance Interpretation in Europe: An Update

Charlotte Charpentier,1 Ricardo Camacho,2 Jean Ruelle,3 Rolf Kaiser,4 Josef Eberle,5 Lutz Gürtler,5 Alejandro Pironti,6 Martin Stürmer,7, Françoise Brun-Vézinet,1 Diane Descamps,1 and Martin Obermeier6
HIV - Diagnostics

HIV-1/2 Antigen/Antibody Immunoassay

(+)

(-) Negative for HIV-1 and HIV-2 antibodies and p24 Ag

HIV-1/HIV-2 Ab Differentiation Immunoassay

HIV-1 (+) HIV-2 (-) HIV-1 antibodies detected

HIV-1 (-) HIV-2 (+) HIV-2 antibodies detected

HIV-1 (+) HIV-2 (+) HIV antibodies detected

HIV-1 (-) or Indeterminate HIV-2 (-)

HIV-1 NAT

HIV-1 NAT (+) Acute HIV-1 infection

HIV-1 NAT (-) Negative for HIV-1

https://www.hiv.uw.edu/go/screening-diagnosis/diagnostic-testing/core-concept/all.
Guidelines
„Care of HIV-2 positive individuals in Europe“
diagnostics - antibodies

Initial screening: standard antibody screening tests (3rd and 4th generation)

Confirmatory assays (antibody differentiation assays) can distinguish between HIV-1 and HIV-2 infection and can be thus used to identify HIV dual infections.
Guidelines
„Care of HIV-2 positive individuals in Europe“
diagnostics - NAT

- HIV-2 plasma viral load analysis should not be used for verifying the presence of HIV-2 infection since plasma viral load may be below the detection limit even in the absence of antiretroviral therapy (ART).

- HIV-1/HIV-2 coinfections ("dual" infections) are rare and represent about 0.1% of new HIV infections in France.¹

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antigen (viral RNA) | • a portion of HIV-2+ produce no (detectable) plasma RNA  
| • lower plasma viral load

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Guidelines
„Care of HIV-2 positive individuals in Europe“
„When to start treatment?“

Recommendations for HIV-1 (adults, WHO 2015):
“ART should be initiated in all adults living with HIV at any CD4 cell count” (strong recommendation)

Recommendations for HIV-2 (more sophisticated):
France, UK, USA guidelines:
• „don’t treat all“ -> different categories of patients
• based on distinctions in features of HIV-1 and HIV-2
HIV-2 – a „milder cousin“?

- Clinical course of HIV-positive Senegalese sex workers 1985 -1993 HIV-1 (32/46) HIV-2(33/103)*

*) Marlink et al Reduced Rate of Disease Development After HIV-2 Infection as Compared to HIV-1 Science Sept. 1994

CDC IV
disease-free survival

Years of observation

Disease-free survival probability

HIV-2

HIV-1

Dirk Berzow Care for HIV-2+ individuals
2018
**HIV-2: survival & plasma viral load**

**Caio Cohort, Guinea-Bissau** prospective study, rural area, 1991-2009 (18 y), 133 HIV-2+, 158 HIV-

Schim van der Loeff MF Undetectable plasma viral load predicts normal survival... Retrovirology 2010 7-46
HIV-2 & CD4-cell decline (without ART)

ANRS CO3 HIV-1 cohort vs ANRS CO5 HIV-2 cohort (418 HIV-1 and 209 HIV-2)

CD4-cell counts decreased less rapidly in untreated HIV-2 patients than in untreated HIV-1 patients

- HIV-2: 9 cells/ml/year
- HIV-1: 49 cells/ml/year

HIV-2: Progressors and Nonprogressors, Controllers and LTNP

HIV-Controllers prevalence 9.1% (6.3–12.7)
(i.e. controlling HIV replication in the absence of antiretroviral treatment for at least 10 years. 8.8% elite controllers)

LTNPs prevalence 6.1% (95% c.i. 3.9–9.1)
(i.e. asymptomatic for at least 8 years while maintaining CD4 cell count at least 500 cells/ml)

HIV controllers and LTNPs were 10–40-fold more frequent among HIV-2-infected patients

342 HIV-2-infected patients of the ANRS CO5 HIV-2 cohort, 2011
Thiebaut et al Long-term nonprogressors and elite controllers in the ANRS CO5 HIV-2 cohort, AIDS 2011
### CD4-cell recovery after treatment start – same as in HIV-1?

#### HIV-2

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Country</th>
<th>Year</th>
<th>CD4 Recovery</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI/r</td>
<td>Europe</td>
<td>2011</td>
<td>+76 cells/µL/year</td>
<td>61% LPV/r, 13% SQV/r</td>
</tr>
<tr>
<td>INSTI</td>
<td>Europe</td>
<td>2017</td>
<td>+87 cells/µL/year</td>
<td>RAL</td>
</tr>
<tr>
<td>PI/r</td>
<td>West Africa</td>
<td>2016</td>
<td>+191 cells/µL/year</td>
<td>LPV/r “preferred”</td>
</tr>
<tr>
<td>INSTI</td>
<td>Senegal</td>
<td>2017</td>
<td>+161 cells/µL/year</td>
<td>E/c/T/F</td>
</tr>
</tbody>
</table>

#### HIV-1

**Median CD4 Cell Count After Starting ART**

- **n=5299, 7 years of antiretroviral therapy**

![Graph showing median CD4 cell count](image)

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**References**

- Selly Ba, Dana N Raugi, Robert A Smith, A trial of fixed dose combination of elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate for the initial treatment of HIV-2 infection. Abstract MOPEB0294 IAS 2017
- Gras L, Kesselring AM, Griffin JT, et al. CD4 cell counts of 800 cells/mm³ or greater after 7 years of highly active antiretroviral therapy are feasible in most patients starting with 350 cells/mm³ or greater. J Acquir Immune Defic Syndr. 2007;45:183-92

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**2011-2017**

- Dirk Berzow Care for HIV-2+ individuals

2018
### „How to start“? HIV-2 active agents

<table>
<thead>
<tr>
<th>Effective Drugs</th>
<th>Ineffective Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTI</strong></td>
<td></td>
</tr>
<tr>
<td>Tenofovir, lamivudine, emtricitabine, abacavir, zidovudine, stavudine, didanosine, foscarnet</td>
<td>NVP, EFV, RPV, ETV</td>
</tr>
<tr>
<td><strong>NNRTI</strong></td>
<td></td>
</tr>
<tr>
<td>Darunavir, lopinavir, saquinavir</td>
<td>Atazanavir, fosamprenavir, tipranavir, indinavir</td>
</tr>
<tr>
<td><strong>Protease Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Raltegravir, elvitegravir, dolutegravir</td>
<td></td>
</tr>
<tr>
<td><strong>Integrase Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>CCR5 antagonist maraviroc (R5-tropism)</td>
<td>Fusion Inhibitor enfurvitide</td>
</tr>
</tbody>
</table>

Menendes-Arias 2014, Antiretroviral therapy and drug resistance in human immunodeficiency virus type 2 infection, Antiviral Research
Guinea-Bissau police cohort: survival & time to AIDS (HIV-1 vs HIV-2)

Guinea-Bissau Police Cohort, disease progression & AIDS
“HIV’s milder cousin may be less mild as previously thought...”

Progression to AIDS happened at a higher CD4 count with HIV-2 than HIV-1

Average CD4 count at AIDS diagnosis:
• 237 cells/mm³ in people with HIV-2
• 137 cells/mm³ in people with HIV-1

Is HIV-2 a „milder cousin“ or a natural human model of attenuated HIV infection?

**Virus:**
- lower:
  - replication rate
  - plasma-RNA (VL 30-100x lower)
  - VL in genital fluids
- many patients below LOD
- diff. in genetics (*nef, tat, vpx*)

**Host:**
- longer progression time to death
- AIDS
- progressors & nonprogressors
- lower transmission rates
  - sexual transmission
  - MTCT
  - breast feeding

**Immune system:**
- milder alterations
  - cellular
    - CD4
    - CD8
  - humoral: nAb
  - innate immune system
  - immune activation

**Reduced treatment options**
„Care of HIV-2 positive individuals in Europe“
Recommendations - Treatment start

- **Always indicated**: Symptomatic patients, i.e., those with specific HIV-related conditions (CDC category B or C)

- **Should be considered**: Asymptomatic patients with any of the following conditions:
  - CD4 cell count less than 500 CD4 cells/µL blood
  - CD4 cell decrease of more than 30 cells/µL/year, over a period of more than 2 years
  - repeatedly detectable HIV-2 RNA in plasma
  - comorbidities: chronic HBV-, HCV infection

- **Treatment can be delayed**: asymptomatic patients, fulfilling the criteria for HIV-2-long-term non-progressors, i.e.
  - stable CD4 cell counts of more than 500/µL
  - undetectable plasma viral load

Due to the reduced viral load in blood and genital secretions, treatment as prevention (TasP) of sexual transmission of HIV-2 is less relevant than for HIV-1.
For wild type viruses without protease resistance-associated mutations (RAMs) a DVR once -daily dosing seems favorable (Matheron et al, personal data from French cohort). For those viruses with intermediate resistance to DRV (presence of at least one of the RAMs I84V or L90M; see Appendix 2) INSTI should be considered as first choice, and if this is not possible, DRV should be administrated twice daily.

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<table>
<thead>
<tr>
<th>Backbone (NRTIs)</th>
<th>Third drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAF/TDF + FTC or ABC + 3TC or TAF + 3TC</td>
<td><strong>plus</strong> 1 INSTI as RAL, DTG, EVG/c</td>
</tr>
<tr>
<td></td>
<td>1 PI as DRV/r or DRV/c, or alternatively LPV/r</td>
</tr>
</tbody>
</table>

(3TC – lamivudine; ABC – abacavir; c – cobicistat; DRV – darunavir; DTG – dolutegravir; EVG – elvitegravir; FTC – emtricitabine; LPV – lopinavir; r – ritonavir; RAL – raltegravir; TAF – tenofovir alafenamide; TDF – tenofovir disoproxil fumarate).
Definition “treatment failure”:
clinical, immunological and/or virological treatment failure

Recommended drugs for second-line treatment
(results of genotypic resistance testing/ evaluation of the causes of failure, i.e. tolerance, adherence etc):

Active drugs (first line) ± saquinavir (SQV), azidothymidine (AZT), maraviroc (MVC)

MVC: tropism testing can be performed either phenotypically (e.g. via TZM-bl cells) or genotypically in specialised laboratories by env-gene nucleic acid sequencing
„Care of HIV-2 positive individuals in Europe“
NRTI resistance mutations

<table>
<thead>
<tr>
<th>NRTI</th>
<th>high level of resistance</th>
<th>intermediate level of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT</td>
<td>Q151M</td>
<td>S215ACFLY</td>
</tr>
<tr>
<td></td>
<td>S215ACFLY + 1 of (N69ST, K70R, Y115F, K223R)</td>
<td></td>
</tr>
<tr>
<td>3TC/FTC</td>
<td>M184VI</td>
<td>K65R</td>
</tr>
<tr>
<td>ABC</td>
<td>Q151M, K65R</td>
<td>2 of (M184VI, S215ACFLY, D67N, K70RN)</td>
</tr>
<tr>
<td></td>
<td>M184VI + 1 of (L74V, Y115F)</td>
<td></td>
</tr>
<tr>
<td>TDF/TAF</td>
<td>K65R, Q151M+V111</td>
<td></td>
</tr>
</tbody>
</table>

HIV-2 resistance according to the HIV-2EU group resistance interpretation rule set update 2018
HIV-2 resistance according to the HIV-2EU group resistance interpretation rule set update 2018

<table>
<thead>
<tr>
<th>PI</th>
<th>high level of resistance</th>
<th>intermediate level of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>SQV</td>
<td>G48V L90M</td>
<td>I84V</td>
</tr>
<tr>
<td>LPV</td>
<td>2 of (I82F, I84V, L90M) I54M V47A</td>
<td>V62A+ L99F 1 of (I82F, I84V, L90M)</td>
</tr>
<tr>
<td>DRV</td>
<td>I50V I54M I84V + L90M</td>
<td>1 of (I84V, L90M)</td>
</tr>
</tbody>
</table>
### Care of HIV-2 positive individuals in Europe

**INSTI resistance mutations**

<table>
<thead>
<tr>
<th>INSTI</th>
<th>high level of resistance</th>
<th>intermediate level of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAL</td>
<td>N155HR</td>
<td>E92Q</td>
</tr>
<tr>
<td></td>
<td>Q148KR</td>
<td>Y143CGR</td>
</tr>
<tr>
<td></td>
<td>1 of (E92Q, T97A) +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Y143CGR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>E92Q + T97A</td>
<td></td>
</tr>
<tr>
<td>EVG</td>
<td>E92QG</td>
<td>Y143C</td>
</tr>
<tr>
<td></td>
<td>Q148KR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T97A + Y143C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N155H</td>
<td></td>
</tr>
<tr>
<td>DTG</td>
<td>G140S + Q148R</td>
<td>Q148R</td>
</tr>
<tr>
<td></td>
<td>Q148K</td>
<td>N155H</td>
</tr>
<tr>
<td></td>
<td>E92Q + N155H</td>
<td>E92Q</td>
</tr>
<tr>
<td></td>
<td>T97A + N155H</td>
<td>Y143C + T97A</td>
</tr>
</tbody>
</table>

**HIV-2 resistance according to the HIV-2EU group resistance interpretation rule set update 2018**
Guidelines
„Care of HIV-2 positive individuals in Europe“
Pregnancy

Adaption of French and German Guidelines (Pregnancy, Newborn-PEP)

Consideration
- maternal and fetal safety
- active drugs to HIV-2
- option: PI mono (non-progressors, 3rd trimester, DRV/r bid)

Caveats
- Few data are available on the safety for cobicistat, elvitegravir and tenofovir alafenamide.
- No increased maternal or infant morbidity was detected in retrospective studies of dolutegravir during pregnancy.
- So far, there is more clinical experience in treating pregnant women with NRTIs and PIs.
Conclusions

- HIV-2 is rare in Europe
- HIV-2 is different
- HIV-2 treatment is different

- there are guidelines for the care of HIV-2 positive individuals in Europe:
  - diagnostics
  - monitoring
  - treatment start
  - first line therapy (active agents)
  - second line therapy
  - resistance & tropism testing
  - pregnancy
  - PEP
HIV-2: Guidelines Expert Group

Sophie Matheron 2, Rolf Kaiser 4), Martin Obermeier 5), Lutz Guertler 6), Josef Eberle 6), Diane Descamps 2, 7), Charlotte Charpentier 2, 7), Matthias Döring 8), Jan Ruelle 9), Ninon Taylor 10), Martin Stürmer 11), Björn Jensen 12), Jürgen Rockstroh 13), Dirk Berzow 1, and Ricardo Camacho 14)

HIV-2 ARNS Network: Sophie Matheron, Charlotte Charpentier, Diane Descamps

Ricardo Camacho Rega Institute for Medical Research Leuven, Belgium

1) Praxis for Infectiology, Hamburg, Germany, 2) Infectious Diseases Department, Bichat Claude Bernard Hospital, Assistance Publique des Hopitaux de Paris, Paris, France, 3) UMR 1137 IAME, INSERM, Université Paris Diderot, Sorbonne Paris Cité, 4) Institute of Virology, University of Cologne, Germany, 5) Medical Center for Infectious Diseases, Berlin, Germany, 6) Max von Pettenkofer Institute for Hygiene and Medical Microbiology, University of München, Munich, Germany, 7) Virology Department, Bichat Claude Bernard Hospital, Assistance Publique des Hopitaux de Paris, Paris, France, 8) Department for Computational Biology and Applied Algorithmics, MaxPlanck Institute for Informatics, Saarland Informatics Campus, Saarbrücken, Germany, 9) Université catholique de Louvain, AIDS Reference Laboratory, Brussels, Belgium, 10) IIIrd Medical Department with Hematology, Medical Oncology, Hemostaseology, Rheumatology and Infectious Diseases, Laboratory of Immunological and Molecular Cancer Research (LIMCR) Center for Clinical Cancer and Immunology Trials Private Medical University Hospital Salzburg, Austria, 11) IMD Medizinisches Versorgungszentrum, Frankfurt, Germany, 12) Klinik für Gastroenterologie, Hepatologie und Infektiologie, Universitätsklinikum Düsseldorf, Germany, 13) Department of Medicine I, University of Bonn, Bonn, Germany, 14) Clinical and Epidemiological Virology, Rega Institute for Medical Research, Department of Microbiology and Immunology, Leuven, Belgium
The H₂O project

H₂O :
HIV-2 in Europe: Observation of the care situation of HIV-2 positive individuals in
  • Hamburg HIV care centers
  • German HIV care centers
  • ???

1. Overview and description
Questionaire of health care workers (doctors)
  • numbers of patients
  • numbers of nonprogressors
  • treatment (start, first line, response, second line, salvage, resistance)
  • retention rate and follow up

2. Option:
  • prospective cohort
  • (biobank ?)
Thank you for your attention ...
back up
The „scientific“ HIV-2-world

Africa:

**Senegal:** Fann, Ndour, Sow U1) Marlink U2) MCR, WAPHIR

**The Gambia** Banjul (Fajara) Jallow, Cotton, de Silva, Whittle, Rowland-Jones
GB1) *)NL1) Togun

**Guinea-Bissau** Poulsen (D)
Caio: Rowland-Jones, Whittle NL1)
GB1) GB2)
The Bissau HIV cohort study g.
Police Cohort, daSilva, Es. GB3)

**IeDEA West Africa**
Benin, Gambia, Mali, Nigeria, Senegal, Togo, Côte d’Ivoire, Guina Bissau, Tchounga, Ekouevie F1) U1) F2)
n=1825

**Burkina Faso**
Sanou

Europe:

**HIV-2 EU Expert group:** Resistance pattern interpretation rule set

**France**
F1) ARNS HIV-2 COS Cohort, Benard, B.-V., Charpentier, Descamps, Damond, Matheron, Visseaux n > 1000
F, B, L, NL, I, P, SP, SW: ACHIEV2E-Collaboration
Damond, Ruelle n=70
F2) INSERM Bordeaux Peeters, Dabis, Balestre, Drylewicz

**Portugal** div./Camacho

**Belgium** Ruelle

**Spain** Trevino, Soriano

USA:

**U1) University Washington**
Raugi, Gottlieb

**U2) Boston Marlink**
HIV-2
### HIV-2 & diagnostic procedures

<table>
<thead>
<tr>
<th>antibodies</th>
<th>epitopes: distinctions env&gt;pol&gt;gag</th>
</tr>
</thead>
<tbody>
<tr>
<td>antigen (viral RNA)</td>
<td>a portion of HIV-2+ are controllers/nonprogressors ((\Rightarrow) no plasma RNA)</td>
</tr>
<tr>
<td>antigen</td>
<td>lower plasma viral load in general</td>
</tr>
</tbody>
</table>

**Gene and Product**

<table>
<thead>
<tr>
<th>Gene and Product</th>
<th>HIV-1</th>
<th>HIV-2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>env</strong></td>
<td></td>
<td></td>
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<tr>
<td>Precursor Protein</td>
<td>gp160</td>
<td>gp140</td>
</tr>
<tr>
<td>External Glycoprotein</td>
<td>gp120</td>
<td>gp105/125</td>
</tr>
<tr>
<td>Transmembrane Protein</td>
<td>gp41</td>
<td>gp36/41</td>
</tr>
<tr>
<td><strong>pol</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reverse Transcriptase</td>
<td>p66</td>
<td>p68</td>
</tr>
<tr>
<td>Reverse Transcriptase</td>
<td>p51</td>
<td>p53</td>
</tr>
<tr>
<td>Endonuclease</td>
<td>p31</td>
<td>p31/34</td>
</tr>
<tr>
<td><strong>gag</strong></td>
<td></td>
<td></td>
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<tr>
<td>Gag Precursor</td>
<td>p55</td>
<td>p56</td>
</tr>
<tr>
<td>Core</td>
<td>p24</td>
<td>p26</td>
</tr>
<tr>
<td>Matrix</td>
<td>p17</td>
<td>p16</td>
</tr>
<tr>
<td>Nucleocapsid Precursor</td>
<td>p15</td>
<td>p15</td>
</tr>
</tbody>
</table>

https://www.hiv.uw.edu/go/screening-diagnosis/diagnostic-testing/core-concept/all.
Dirk Berzow Care for HIV-2+ individuals
2018
HIV - Diagnostics

HIV-1/2 Antigen/Antibody Immunoassay

(+)
Negative for HIV-1 and HIV-2 antibodies and p24 Ag

(-)

HIV-1/HIV-2 Ab Differentiation Immunoassay

HIV-1 (+) HIV-2 (-) HIV-1 antibodies detected
HIV-1 (−) HIV-2 (+) HIV-2 antibodies detected
HIV-1 (+) HIV-2 (+) HIV antibodies detected
HIV-1 (−) or Indeterminate HIV-2 (−)

HIV-1 NAT

HIV-1 NAT (+) Acute HIV-1 infection
HIV-1 NAT (−) Negative for HIV-1

Immunoblot (IB), Western blot (WB), Line-Immuno-Assay (LIA), Antibody differentiation assay

https://www.hiv.uw.edu/go/screening-diagnosis/diagnostic-testing/core-concept/all.

Dirk Berzow Care for HIV-2+ individuals
2018
HIV-1/HIV-2 differentiation assay

Immunoblot (IB), Western blot (WB), Line-Immuno-Assay (LIA), or Antibody differentiation assay

Geenius HIV1-/HIV-2 Supplemental Assay

MultispotHIV1-/HIV-2 Test
HIV-2: Transmitted drug resistance?

ANRS CO5 HIV-2 Cohort, France:

• prevalence of transmitted drug resistance was 5.0%

• mutations were detected only in protease (V47A, I82F)

• surveys conducted reported HIV-2 TDR of 5.6% in the Ivory Coast and 3.3% in Portugal

Charlotte Charpentier, Transmitted drug resistance in French in HIV-2-infected patients, AIDS 2013, 27:1671–1677
Guidelines

„Care of HIV-2 positive individuals in Europe“

Pregnancy

If a pregnant woman is already under an antiretroviral treatment with drugs that are active against HIV-2, the treatment should be continued.

Few data are available on the safety for cobicistat, elvitegravir and tenofovir alafenamide. No increased maternal or infant morbidity was detected in retrospective studies of dolutegravir during pregnancy.

Pregnant women fulfilling any of the criteria mentioned in “recommended treatment start” should start treatment with the recommended drugs for first-line HIV-2-ART from week 12-15 onwards.

So far, there is more clinical experience in treating pregnant women with NRTIs and PIs.
“HIV’s milder cousin may be less mild as previously thought…”

Joakim Esbjörnsson, CROI 2017

Guinea-Bissau police cohort
• initiated 1990, 4820 members,
• HIV-1 (225) and HIV-2 (87)
• ART available since 2006

HIV-2 & CD4-cell decline (without ART)

ANRS CO3 HIV-1 cohort vs ANRS CO5 HIV-2 cohort (418 HIV-1 and 209 HIV-2)

CD4-cell counts decreased less rapidly in untreated HIV-2 patients than in untreated HIV-1 patients

- **HIV-2**: 9 cells/ml/year
- **HIV-1**: 49 cells/ml/year


“Guinea-Bissau police cohort” HIV-1 (225) and HIV-2 (87)

Average CD4 decline:

- **HIV-2**: 12.8 cells/ml/year
- **HIV-1**: 22.5 cells/ml/year

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Participants</th>
<th>Year</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACHIEV2E, France</td>
<td>France</td>
<td>n=168</td>
<td>2011</td>
<td>Triple NUK/PI/r</td>
</tr>
<tr>
<td>IeDEA, West Africa</td>
<td>West Africa</td>
<td>n=422</td>
<td>2016</td>
<td>Triple NUK/PI/PI/r</td>
</tr>
<tr>
<td>Ba, Raugi, Gottlieb, Senegal</td>
<td>Senegal</td>
<td>n=29</td>
<td>IAS 2017</td>
<td>INSTI (EVG/c/TDF/FTC)</td>
</tr>
<tr>
<td>ANRS 159, France</td>
<td>France</td>
<td>n=30</td>
<td>CROI 2017</td>
<td>INSTI (RAL/TDF/FTC)</td>
</tr>
</tbody>
</table>
ACHIEV2E Collaboration Study Group, 2011

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Description</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple NRTI therapy</td>
<td>73% ABC 3TC AZT 7% DDI 3TC AZT</td>
<td>44 patients</td>
</tr>
<tr>
<td>PI/r therapy</td>
<td>61% LPV/r 13% SQV/r</td>
<td>126 patients</td>
</tr>
</tbody>
</table>

- **Triple NRTI**
  - CD4 cells: +16 cells/ml/month during the early phase, -60 cells/ml/year during the second phase
  - Undetectable RNA 11% (12 month), mean RNA 4.0 c/ml

- **PI/r**
  - CD4 cell count slopes: +12 cells/ml/month during the early phase, +76 cells/ml/year during the second phase
  - Undetectable RNA 79% (12 month), mean RNA 2.20 c/ml

PI/r regimens were associated with better CD4 cell count and HIV-2 RNA level outcomes, compared with NRTI regimens.

Baseline: median CD4 cell count was 191 cells/ml, median plasma HIV-2 RNA level was 2.7 log10 copies/ml

Benard 2011 Immunovirological Response to Triple Nucleotide Reverse-Transcriptase Inhibitors and Ritonavir-Boosted Protease Inhibitors in Treatment-Naive HIV-2–Infected Patients: The ACHIEV2E Collaboration Study Group
CD4-cell recovery after treatment start

Triple NRTI
- +16 cells/ml/month during the early phase
- -60 cells/ml/year during the second phase
- undetectable RNA 11% (12 month), mean RNA 4.0 c/ml

PI/r,
- +12 cells/ml/month during the early phase
- +76 cells/ml/year during the second phase
- undetectable RNA 79% (12 month), mean RNA 2.2.0 c/ml

Triple NRTI therapy
- 44 patients, 73% ABC 3TC AZT 7% DDI 3TC AZT
PI/r therapy
- 126 patients, 61% LPV/r 13% SQV/r

baseline: median CD4 cell count was 191 cells/ml, median plasma HIV-2 RNA level was 2.7 log10 copies/ml
PI/r regimens were associated with better CD4 cell count and HIV-2 RNA level outcomes, compared with NRTI regimens.

Benard 2011 Immunovirological Response to Triple Nucleotide Reverse-Transcriptase Inhibitors and Ritonavir-Boosted Protease Inhibitors in Treatment-Naive HIV-2–Infected Patients: The ACHIEV2E Collaboration Study Group
CD4-cell recovery after starting ART 2016, IeDEA, n=422

**Figure 2.** Mean adjusted CD4 count change after antiretroviral treatment initiation according to baseline CD4 count (2a – top panel) and by antiretroviral treatment regimen (2b – bottom panel), IeDEA West Africa Collaboration.
Caio Cohort
Guinea-Bissau

prospective study, rural, villagers, 1991-2009
133 HIV-2-positive and 158 HIV-negative

• HIV-2+: Age 47 y, VL 347 c/ml CD4 29%
• 37% HIV-2 RNA < 100 c/ml
• 17% HIV-2 > 10,000 c/ml
• mortality rate HIV-2: 4.5 /100 py, (CI 3.6-5.5), compared to 2.1 in HIV-negative (1.6-2.9)
1. LFU: 6.7% (6.3%)
2. 12.8% became HIV-1 infected
Table 3: Crude mortality rates by age and sex among HIV-2 - infected and HIV uninfected individuals.

<table>
<thead>
<tr>
<th>Age group</th>
<th>HIV-2 infected</th>
<th>HIV-uninfected</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number died/ total per category (%)</td>
<td>Mortality rate per 100 person-years (95% CI)</td>
<td>Number died/ total per category (%)</td>
</tr>
<tr>
<td>&lt;40</td>
<td>15/37 (41)</td>
<td>3.4 (2.0, 5.6)</td>
<td>7/56 (13)</td>
</tr>
<tr>
<td>40-59</td>
<td>23/59 (39)</td>
<td>3.4 (2.3, 5.1)</td>
<td>15/63 (24)</td>
</tr>
<tr>
<td>≥ 60</td>
<td>28/36 (78)</td>
<td>8.5 (5.9, 12.3)</td>
<td>27/39 (69)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27/42 (64)</td>
<td>6.1 (4.2, 8.8)</td>
<td>20/43 (46)</td>
</tr>
<tr>
<td>Female</td>
<td>39/91 (43)</td>
<td>3.9 (2.8, 5.3)</td>
<td>29/115 (25)</td>
</tr>
<tr>
<td>Calendar time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1991-1998</td>
<td>37/133 (28)</td>
<td>4.3 (3.1, 6.0)</td>
<td>24/158 (15)</td>
</tr>
<tr>
<td>1999-2009</td>
<td>29/84 (35)</td>
<td>4.8 (3.4, 7.0)</td>
<td>25/120 (21)</td>
</tr>
<tr>
<td>Overall</td>
<td>66/133 (50)</td>
<td>4.5 (3.6, 5.8)</td>
<td>49/158 (31)</td>
</tr>
</tbody>
</table>

a Age at enrolment
b Missing data for one individual
### HIV-2 Mortality, CD4, PVL, compared to HIV-1

**TABLE 3. Association of Baseline PVL and CD4% With Mortality**

<table>
<thead>
<tr>
<th>Baseline Value</th>
<th>HIV-1 Infected</th>
<th>HIV-2 Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Subjects</td>
<td>No. (%) Deaths</td>
</tr>
<tr>
<td>Overall</td>
<td>101</td>
<td>32 (32)</td>
</tr>
<tr>
<td>PVL (RNA copies/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1000</td>
<td>6</td>
<td>1 (17)</td>
</tr>
<tr>
<td>1000–9999</td>
<td>26</td>
<td>7 (27)</td>
</tr>
<tr>
<td>10,000–99,999</td>
<td>54</td>
<td>17 (31)</td>
</tr>
<tr>
<td>≥100,000</td>
<td>8</td>
<td>4 (50)</td>
</tr>
<tr>
<td>CD4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;28%</td>
<td>56</td>
<td>14 (25)</td>
</tr>
<tr>
<td>14–28%</td>
<td>26</td>
<td>11 (42)</td>
</tr>
<tr>
<td>&lt;14%</td>
<td>6</td>
<td>4 (67)</td>
</tr>
</tbody>
</table>

*Comparing HIV-2 with HIV-1.
†Mantel–Haenszel combined mortality rate ratio, controlling for PVL.
‡Mantel–Haenszel combined mortality rate ratio, controlling for CD4%.

J Acquir Immune Defic Syndr 2005;38:335–341
Baseline Plasma Viral Load and CD4 Cell Percentage Predict Survival in HIV-1– and HIV-2–Infected Women in a Community-Based Cohort in The Gambia Hansmann, Schim van der Loeff, Whittle et al
HIV-2, CD4-cell decline (compared to HIV-1)

Table 3. Association between the annual rate of CD4+ T cell decline and baseline plasma RNA viral load among subjects with baseline CD4+ T cell counts >200 cells/μL.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subjects infected with HIV-1 (n = 120)</th>
<th>Subjects infected with HIV-2 (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline plasma HIV RNA level, copies/mL</td>
<td>Yearly decline in CD4+ T cell levels, % (95% CI)</td>
<td>Yearly decline in CD4+ T cell levels, % (95% CI)</td>
</tr>
<tr>
<td>&lt;100</td>
<td>6 (5)</td>
<td>28 (57)</td>
</tr>
<tr>
<td>100–999</td>
<td>5 (4)</td>
<td>14 (29)</td>
</tr>
<tr>
<td>1000–9999</td>
<td>31 (26)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>10,000–99,999</td>
<td>42 (35)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>≥100,000</td>
<td>36 (30)</td>
<td>0</td>
</tr>
<tr>
<td>Median rate</td>
<td>15.9 (11.1–20.3)</td>
<td>4.1 (–0.5 to 9.2)</td>
</tr>
<tr>
<td>Median rate per log₁₀ RNA viral load</td>
<td>4.1 (2.7–5.4)</td>
<td>3.3 (0.9–5.5)</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval.

Equal Plasma Viral Loads Predict a Similar Rate of CD4+ T Cell Decline in Human Immunodeficiency Virus (HIV) Type 1– and HIV-2–Infected Individuals from Senegal, West Africa
Geoffrey S. Gottlieb,1 Papa Salif Sow,7 Stephen E. Hawes,2,5 Ibra Ndoye,8 Mary Redman,4 Awa M. Coll-Seck,7 Mame A. Faye-Niang,7 Aissatou Diop,7 Jane M. Kuypers,2 Cathy W. Critchlow,5 Richard Respess,6 James I. Mullins,1,3 and Nancy B. Kiviat1,2
JID 2002;185 (1 April)
HIV-2 and CD4-cell characteristics: 
decline (without ART) and recovery (under ART)

CD4-cell counts decreased less rapidly in untreated HIV-2 patients than in untreated HIV-1 patients
  • HIV-2: 9 cells/ml/year
  • HIV-1: 49 cells/ml/year

After initiating first-line ART (59 HIV-1 and 63 HIV-2), CD4 increase was:
  • during the first 2 months of treatment,
    • HIV-2: 24 cells/ml/month
    • HIV-1 59 cells/ml/month
  • after the first 2 months of treatment,
    • HIV-2 - 3 cells/ml/year
    • HIV-1 46 cells/ml/year

ANRS CO3 HIV-1 cohort vs ANRS CO5 HIV-2 cohort (418 HIV-1 and 209 HIV-2)

HIV-2 Therapie
ANRS CO5 HIV-2 Cohort 61 patients

- 61 ART-naïve patients treated median 136 c/µl,
- **12/24 month ART** (adequate plasma drug level) +72 c/µl, + 68 c/µl
- **12/24 month ART** (inadequate plasma drug level) + 9 c/µl, + 45/µl

- very poor increase in CD4 cell count (+ 45 in first month, + 10 next 12 month)
- **55% HIV2-RNA < 100**, 5 deaths, 3 AIDS, PI = triple NUC
- increased apoptosis and decreased thymic regeneration like in HIV-1-infected patients?
- HIV-2: less apoptosis
- proliferative T-cell responses to HIV-2 similar to HIV-1-specific T-cell-response in HIV LTNPs
- HIV-2 viral load lower than HIV-1, HIV-2 proviral DNA levels similar

Matheron S, CD4 cell recovery in treated HIV-2 infected adults is lower than expected…. AIDS, 2006 Feb 14;20(3): 459-62,
### HIV-2 therapie

Poor CD4-cell recovery after starting ART

ANRS CO5(HIV-2) cohort:

- Drylewicz J, Comparision of viro-immunological marker changes between HIV-1 and HIV-2 infected patients in France AIDS 2008 Feb 19;22(4): 457-68

<table>
<thead>
<tr>
<th>Table 4. Estimated mean (95% confidence interval) slopes from linear mixed models for patients starting combination antiretroviral therapy from ANRS CO3 Aquitaine and ANRS CO5 HIV-2 cohorts.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Naive starting CART</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Slope during first 2 months</strong></td>
</tr>
<tr>
<td>CD4 cell count/μl/month</td>
</tr>
<tr>
<td>CD4%/month</td>
</tr>
<tr>
<td>Viral load in log_{10} copies/ml/month</td>
</tr>
<tr>
<td>CD8 cell count/μl/month</td>
</tr>
<tr>
<td>CD4:CD8 ratio/month</td>
</tr>
<tr>
<td><strong>Slope after first 2 months</strong></td>
</tr>
<tr>
<td>CD4 cell count/μl/year</td>
</tr>
<tr>
<td>CD4%/year</td>
</tr>
<tr>
<td>Viral load in log_{10} copies/ml/year</td>
</tr>
<tr>
<td>CD8 cell count/μl/year</td>
</tr>
<tr>
<td>CD4:CD8 ratio/year</td>
</tr>
</tbody>
</table>

CART, Combination antiretroviral therapy.

*Comparison between HIV-1 and HIV-2.*
Benard 2011 Immunovirological Response to Triple Nucleotide Reverse-Transcriptase Inhibitors and Ritonavir-Boosted Protease Inhibitors in Treatment-Naive HIV-2–Infected Patients: The ACHIEV2E Collaboration Study Group
CD4-cell recovery after starting ART 2016, IeDEA, n=422
2016, IeDEA, n=422
CD4-cell changes after starting ART

Table 2. Mean CD4 count changes at 6 and 12 months compared to the reference group\(^b\) and estimated with multivariable linear mixed model (N = 422; 1341 observations), IeDEA West Africa Collaboration

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean CD4 change difference (cells/μl) at 6 months (95% CI)</th>
<th>Mean CD4 change difference (cells/μl) at 12 months (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CD4 count (cells/μl)</td>
<td></td>
<td></td>
<td>0.0291</td>
</tr>
<tr>
<td>&lt;50</td>
<td>Reference(^b)</td>
<td>Reference(^c)</td>
<td></td>
</tr>
<tr>
<td>50 to 99</td>
<td>(-6 (-59 to +48))</td>
<td>(-45 (-105 to +16))</td>
<td></td>
</tr>
<tr>
<td>100 to 199</td>
<td>(-6 (-53 to +41))</td>
<td>(-29 (-83 to +24))</td>
<td></td>
</tr>
<tr>
<td>200 to 349</td>
<td>(-18 (-66 to +29))</td>
<td>(-49 (-104 to +5))</td>
<td></td>
</tr>
<tr>
<td>≥350</td>
<td>(-59 (-116 to +1))</td>
<td>(-99 (-164 to +34))</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.0302</td>
</tr>
<tr>
<td>Female</td>
<td>Reference(^b)</td>
<td>Reference(^c)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>(-26 (-54 to +2))</td>
<td>(-39 (-71 to +8))</td>
<td></td>
</tr>
<tr>
<td>First ART regimen</td>
<td></td>
<td></td>
<td>0.0045</td>
</tr>
<tr>
<td>Boosted PI-based</td>
<td>Reference(^b)</td>
<td>Reference(^c)</td>
<td></td>
</tr>
<tr>
<td>Unboosted PI-based</td>
<td>(-42 (-74 to +10))</td>
<td>(-58 (-94 to +23))</td>
<td></td>
</tr>
<tr>
<td>NRTI-based</td>
<td>(-72 (-129 to +16))</td>
<td>(-81 (-148 to +14))</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Females with initial CD4 count <50 cells/μl treated with boosted PI-based regimen; CI, confidence interval; ART, antiretroviral treatment; PI, protease inhibitor; NRTI, nucleoside reverse-transcriptase inhibitors; \(^b\)the mean CD4 count change for the reference group at 6 months was 132 cells/μl (95% CI =89; 176); \(^c\)the mean CD4 count change for the reference group at 12 months was 191 cells/μl (95% CI =142; 241).