HIV-2: A summary of present standard of care and treatment options for HIV-2 infected individuals living in Western Europe

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Summary:

HIV-2 is different from HIV-1 in diagnosis, clinical course and antiretroviral treatment. Due to the poor data situation in the field of HIV-2, we present considerations for reliable testing, monitoring and treatment strategies based on available knowledge and expert opinion.

Abstract

HIV-2 infection is endemic in some countries in West Africa. Due to the lower prevalence in industrialized countries, there is limited experience and knowledge on management of HIV-2 infected individuals in Europe. Compared to HIV-1, there are differential characteristics of HIV-2 regarding diagnostic procedures, clinical course and, most importantly, antiretroviral therapy.

We integrated the published literature on HIV-2 (studies and reports on epidemiology, diagnostics, clinical course, treatment) as well as expert experience in diagnosing and clinical care of HIV-2 infected to provide recommendations for a present standard of medical care of HIV- infected in Western European countries, including an overview of strategies for diagnosis, monitoring and treatment, with suggestions for effective drug combinations for first- and second line treatment, post-exposure prophylaxis and prevention of mother-to-child transmission as well as listings of mutations related to HIV-2 drug resistance- and CCR5/CRCX4 co-receptor tropism.

Keywords

HIV2, HIV-2, standard, antiretroviral therapy, resistance, diagnosis, patient monitoring, care

Introduction

The frequency of HIV-2 is much lower compared to HIV-1. The absolute number of HIV-2 infected individuals worldwide is unknown. Reliable and current data are missing until today. According to the experts the number is estimated at 1-2 millions. [1].
West African Countries were known for the world highest prevalence of HIV-2 in parts of their population, so Guinea-Bissau (up to 4%) [2]. HIV-2 infections have also been reported from Senegal, The Gambia, Sierra Leone and Ivory Coast, and, to a lesser extent, from Cape Verde, Angola, Mozambique and the Goa region in India [1] [3]. In Europe, France and Portugal report the highest prevalence (1,000-2,000 cases respectively) [4], [5].

In contrast to HIV-1, there are only limited data on the value of diagnostic tools, monitoring and treatment for HIV-2 infected patients. Published HIV-2 guidelines are available from France [5], Great Britain [6], Portugal [7], Spain [8] and USA [9] dating from 2010 to 2019. To reach a standard we summarize current strategies and tools for the care of HIV-2 infected individuals living in Western Europe.

Diagnosis of HIV-2 infection

Individuals from the aforementioned countries and individuals with high-risk sexual contacts to persons from these countries should be tested for a possible HIV-2 infection or dual infection when HIV antibody tests are reactive.

In general diagnosis of an infection with HIV-2 is more challenging compared to HIV-1, and national HIV Expertise Centers should be contacted if difficulties arise.

For initial screening, standard HIV antibody screening tests (4^{th} generation) are recommended because they detect both HIV-1 and HIV-2 antibodies and antigen. Reactive HIV screening test require confirmatory testing with antibody differentiation assays such as immunoblot (IB), line-immuno-assay (LIA), western blot (WB), or other antibody differentiation assays containing HIV-1 and HIV-2 antigens. Other confirmatory assays such as HIV-1-mono immunoblot or western blot (containing only HIV-1 antigens) may miss an HIV-2 infection due to cross-reactivity. In patients who have been diagnosed with HIV based on ELISA assays who have a low or undetectable HIV-1 viral plasma load in the absence of antiviral therapy one should consider the possible presence of HIV-2 or other HIV-variants and perform additional testing by specific antibody-based confirmatory assays. Patients with an HIV-infection under ART with relevant and constant CD4+ cell loss without detectable HIV-1 plasma RNA should be reevaluated for a possible HIV-2 infection or both HIV-1 and HIV-2 or (as well as other HIV-variants).

Commercially available HIV-1 RNA viral load tests usually do not detect or quantify HIV-2. Most laboratories use in-house assays for HIV-2 viral load determination based on primers and probes in the LTR region [10] . For the European region, two commercial tests kits are available: 1) the *Generic HIV-2 Charge Virale [RUO, research use only]* (Biocentric, Bandol, France) based on TaqMan one-step reverse transcription-quantitative PCR and targets the long terminal repeat and *gag* regions [11] and 2) the *Real Star HIV-2 RUO* (altona Diagnostics, Hamburg, Germany).

HIV-2 plasma viral load analysis should not be used exclusively as confirmation assay as HIV-2 viral load is frequently below the detection limit even in the absence of antiretroviral therapy (ART) [1,12, 13]. While positive HIV-2 PCR results from plasma confirm an HIV-2 infection, a negative PCR result does not exclude the possibility of an HIV-2 infection.

If the serology shows indeterminate results and the HIV-1 and HIV-2 PCRs are both negative, proviral DNA should be used on enriched peripheral blood mononuclear cells. If the type of HIV cannot be cleared, an HIV-2 specialized laboratory should be contacted.

Determination of HIV-2 resistance-associated-mutations (RAMs) can be performed by nucleic acid sequencing. Free-access, web-based interpretation rules or interpretation systems are provided by ARNS (ANRS-AC43 Resistance group genotype interpretation for HIV-2), REGA (Algorithm for the use of genotypic HIV-2 resistance data), Stanford HIV drug resistance database, and HIV-GRADE (described in chapter "*bioinformatics tools*") [14].

In Europe dual infections are rare and represent about 0.1% of new HIV infections in France [15]. They may remain undetected when standard antibody screening and confirmation assays based only on HIV-1 are used. If dual infected individuals are treated with an ART non-effective for HIV-2 (see below), they will show neither clinical improvement nor $CD4^+$-cell count recovery despite HIV-1 plasma RNA undetectability. Hence, samples from such individuals should be promptly re-analyzed to exclude a possible HIV-2 infection.

Characteristics of HIV-2 infection

HIV-2 infection is characterized by a slower rate of disease progression compared to HIV-1 [16,17]. Data from cohorts in West Africa indicate that up to 37% of untreated HIV-2 infected individuals have an undetectable viral load [13] and exhibit long-term survival [12]. In a French study cohort, about half of the untreated patients showed undetectable viral load (VL) while those with viremia had mean VL of 3.0 $\log_{10}$ copies/mL [18]. The estimated annual average decrease in $CD4^+$-cells count was 4.5-fold less pronounced in ART-naive HIV-2 patients than in HIV-1 infected patients, after adjusting for sex, age and geographic origin (decline of 11 versus 49 cells/year) [19]. However, antiretroviral treatment of HIV-2 infection should not be started too late since the immune reconstitution of HIV-2 patients under ART is poorer than in HIV-1 infected patients [19]. Data from the French ANRS CO5 cohort and the European ACHIeV2e network suggest that starting therapy early in the course of infection should allow for an efficient recovery of $CD4^+$-cells [20,21]. The mean observed $CD4^+$-cell count recovery at 12 months after initiating a first-line ART was +105 cells/µL in HIV-2 patients (n=185) in comparison to +202 cells/µl in HIV-1 patients (n=30,231) in the same cohort [21]. The proportion of non-progressors patients in HIV-2 is higher than in HIV-1 infection. Data from the French ANRS CO5 HIV-2 cohort showed that, using the same definition as for HIV-1 infection, 6% of HIV-2 infected individuals are long-term-non-progressors (i.e. asymptomatic for ≥8 years while maintaining $CD4^+$-cell count ≥500 cells/µL), and 9% are elite controllers (i.e. controlling HIV replication in the absence of ART for ≥10 years) [22]. Nevertheless, a notable proportion of HIV-2 infected will finally progress to AIDS if left untreated [23].

Treatment

Monitoring before start of treatment

$CD4^+$-cell count and plasma viral load should be monitored every three months (or at least twice a year) depending on the patient's clinical status, previous $CD4^+$-cell count and the rate of $CD4^+$-cell count decline. Any detectable VL should be confirmed using a subsequent follow-up sample taken one month apart.

Before treatment start, a genotypic resistance test of viral RNA for nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), and integrase inhibitors (INIs), is recommended in case of detectable plasma VL. If VL is too low to be amplified, proviral DNA could be considered. Occurrence of primary resistance was reported for 5 % of patients in France [15, 24] and may dramatically impair the success of treatment. In addition, resistance of HIV-2 develops more rapidly under suboptimal ART and therapy options are more limited compared to HIV-1 [25-27].

Recommended treatment start

A systematic review of ART for HIV-2 infected produced no data from randomized controlled trials guiding ART initiation yet, but such a trial is ongoing in West Africa (ANRS 12294 FIT2 trial). Current national European guidelines[5-8] concur that initiation of ART should be based on $CD4^+$-cell count, viremia and clinical status (see also "*Characteristics of HIV-2 infection*") . Antiretroviral therapy of HIV-2 infection is always indicated in symptomatic patients, i.e., those with specific HIV-related symptoms (CDC category B or C according to the revised CDC classification system for HIV-infected adolescents and adults) [5-9].

Antiretroviral treatment should be considered in asymptomatic patients with any of the following conditions:

- $CD4^+$-cell count ≤500 $CD4^+$-cells/µL blood [5,7]
- $CD4^+$-cell decrease of more than 30 cells/µL and year, over a period of more than three years [5,7]
- Repeatedly detectable HIV-2 RNA in plasma [5,7]
- Comorbidities, such as chronic HBV infection [5].

Treatment may be delayed in asymptomatic patients without any of these criteria, like long-term non-progressors with stable $CD4^+$-cell counts of more than 500 cells/µL and undetectable plasma viral load [5]. However, US-American (DHHS) guidelines recommend treatment start at or soon after HIV-2 diagnosis (unaffected by $CD4^+$-cell count and viral load, as in HIV-1) [9]. This can be an option for HIV-2 patients, either regarding public health care aspects [1] or regarding "Treatment as Prevention" aspects (though the viral load in blood and genital secretions is reduced in HIV-2[27]) and should be discussed with the affected persons on a case-by-case basis.

Recommended drugs – first-line treatment

Selection of an appropriate antiretroviral regimen is challenging due to the limited number of drugs effective against HIV-2 compared to HIV-1:

All NNRTIs, due to the large extent of polymorphisms, and the fusion inhibitor enfuvirtide are ineffective drugs against HIV-2. In addition, the PIs atazanavir, fosamprenavir, indinavir, nelfinavir, and tipranavir have reduced activity against HIV-2. Effective drugs against HIV-2 are all NRTIs, the (boosted) PIs darunavir, lopinavir and saquinavir, all INIs and the CCR5-inhibitor maraviroc in case of CCR5 tropism of the virus [14, 20-21, 25-27, 29, 30].

The recommended first-line treatment for HIV-2 infection should consist of a combination of 2 NRTIs plus a third partner, either an INI or a boosted, active PI (listed in Table 1).

Data on dosing of the boosted PI darunavir (DRV/r) are still limited. For wild-type viruses without protease RAMs DRV/r 800/100 mg once-daily is an option (Matheron Sophie, personal data from the French cohort). In the Portuguese cohort several viral failures of first line regimens with DRV/r 800/100 mg once-daily occurred, with detection of the I50V mutation (Perpetua Gomes, personal data). For those viruses with predicted resistance to DRV (presence of at least one of the RAMs I50V, I54M, I84V and/or L90M; see Appendix, Table 2) INIs should be considered as first choice, and if this is not possible, DRV/r 600/100 mg should be administrated twice daily. No clinical data on DRV/cobicistat (DRV/c) are yet available, but theoretically cobicistat should work as in HIV-1.

INIs are recommended as a first-line treatment mainly due to their *in vivo* efficiency and low side effect profile. There are limited data on integrase inhibitors from clinical practice [31-34]. As in HIV-1, physicians should consider the child bearing potential in women and pay attention to the current recommendations of medical agencies for drug safety.

The few available data on treatment of HIV-1/HIV-2 co-infected patients suggest that ARTs active against both viruses should be chosen. Treatment start should be guided by the recommendations for the HIV-1 infection and monitoring should include viral load and drug resistance testing for both HIV-1 and HIV-2 [35].

Recommended drugs – Second-line treatment

The definition of treatment failure in HIV-2 is more complex than in HIV-1 given the intrinsically low viral loads in non-treated infections and the poor $CD4^+$-cell recovery during treatment and contains combined endpoints regarding VL, CD4+-cell recovery and clinical course.

Treatment failure in HIV-2 can be defined

- as detection of HIV-2 plasma RNA in at least two consecutive analyses,
- decline of $CD4^+$-cell count, which can occur even by undetectable HIV-2 RNA plasma,
- and/or persistence or emergence of HIV/AIDS-specific symptoms [5, 20, 25-27].

In case of therapy failure, the choice of a second-line regimen should be based on the results of genotypic resistance testing and the evaluation of the causes of failure (intolerance, lack of adherence).

Depending on the results of genotyping tests, zidovudine (AZT), maraviroc (MVC), and boosted saquinavir (SQV/r) in combination can be considered as an option for a second-line treatment. When the CCR5-coreceptor inhibitor maraviroc is considered as a treatment option, tropism testing can be performed either phenotypically or genotypically by nucleic acid Sanger sequencing of the gp105 V3 loop region, similarly to HIV-1 [36-37].

HIV-2 RAMs for NRTIs and PIs differ from those for HIV-1 regarding their appearance and significance. The HIV-2EU expert group has published a list of HIV-2 resistance mutations and a standardized HIV-2 drug resistance interpretation rule set [14]. Table 2 in the Appendix provides an updated table of HIV-2 RAMs and Table 3 an overview of features in the V3 loop that are discriminatory for viruses using CCR5 and those that are capable of using CXCR4 according to $\text{geno2pheno}_{[\text{coreceptor-hiv2}]}$.

If the first-line treatment contained a PI, the second-line treatment should contain an INI and *vice versa***,** depending on the results of resistance testing.

Bioinformatic tools for the interpretation of HIV-2 genotypic resistance/tropism data

Drug resistance against HIV-2 can be determined using the HIV-2EU resistance tool (http://www.hiv-grade.de), which determines drug resistance according to the rule set of the HIV-2EU expert group. The French rule set is available via the ANRS-AC43 website (http://www.hivfrenchresistance.org). HIV-2 coreceptor usage can be determined using the statistical model of $\text{geno2pheno}_{[\text{coreceptor-hiv2}]}$ (http://coreceptor-hiv2.geno2pheno.org).

These tools allow the analysis of nucleotide sequences of the relevant genomic regions. To interpret the results, the input sequences are aligned to an HIV-2 reference strain. The HIV-2EU tool evaluates the impact of mutations according to the HIV-2EU rule set [10], while $\text{geno2pheno}_{[\text{coreceptor-hiv2}]}$ uses a linear model that considers all V3 positions [36-37].

Parameter monitoring under treatment

Treatment should be closely monitored to minimize the risk of emergence of viral resistance. There is evidence that the barrier for the development of NRTIs and PIs resistance of HIV-2 is at least partially lower and the time window for a regimen change is narrower than in HIV-1 [25-27]. CD4-cell

count monitoring is relevant, because some HIV-2 patients can deteriorate without detectable HIV-2 viral load [6].

Monitoring is recommended as follows:

- Quantification of HIV-2 viral load and $CD4^+$-cell counts at months 1, 3 and 6 after initiation or change of ART, and subsequently
    - every 3 months if $CD4^+$-cell count is <200 cells/µL
    - every 3 to 6 months when $CD4^+$-cell count is between 200-500 cells/µL or >500 cells/µL depending on patient adherence, clinical status and comorbidities
- Checking adherence
- Resistance testing in case of treatment failure
- In case of clinical progression, plasma viral load and $CD4^+$-cell count should be checked immediately
- Throughout pregnancy: viral load, $CD4^+$-cell count and adherence should be tested every 1 to 3 months

Pregnancy

Regarding maternal and fetal safety, data from HIV-1 treatment can be transferred to HIV-2. If a pregnant woman is already under ART with drugs active against HIV-2 and with no or lowest possible toxicity for the fetus the treatment should be continued. Otherwise, the choice to continue or to switch should be made on a case by case decision, taking into account the mother's HIV clinical status, including results of cumulative genotyping tests, adherence and tolerance to ART.

Treating pregnant women or women of child bearing potential who are not able to use effective contraception throughout treatment imply that the prescriber has to consider all safety information, precautionary statements and caveats regarding ART medication, especially regarding INI (DTG, BIC), PI, cobicistat, and tenofovir alafenamide. The administration of DRV/r twice daily should be considered during the 3rd trimester or earlier, depending on HIV-2 plasma concentration and drug history. So far, there is more clinical experience in treating pregnant women with NRTIs and PIs compared to INIs [38].

Pregnant women fulfilling any of the criteria mentioned in "recommended treatment start" should start treatment with the recommended and suitable drugs for first-line HIV-2-ART from week 12-15 onwards, selecting the safest and best-known substances in terms of potential maternal and fetal toxicity. Regarding to US-American (DHHS) guidelines [9], ART can be offered to all HIV-2 infected pregnant women.

The risk of mother-to-child-Transmission (MTCT) in HIV-2 is lower than in HIV-1, due to the reduced average plasma viral load [38]. To further reduce the MTCT risk, ART from the beginning of the third trimester of pregnancy is recommended also for HIV-2 infected women with undetectable plasma viral load and no comorbidities.

If the viral load is detectable or undetermined shortly before delivery, the addition of RAL to an established ART should be considered and/or a planned caesarean section discussed. In these cases, as well as in cases of delivery complications and increased risk of MTCT intravenous AZT-therapy should be applied perinatally (according to current guidelines for HIV-1).

Post-exposure prophylaxis for the newborn (newborn-PEP) should always been considered. All newborns who were perinatally exposed to HIV-2 (if the mother's plasma viral load was unknown or if the last viral load measurement was above the detection limit) should receive appropriate antiretroviral triple therapy as soon as possible after delivery. If the maternal ultimate viral load

before delivery was undetectable, AZT monotherapy to the newborn can be administered according to current guidelines for HIV-1 and newborn-PEP, as there are no specific data for HIV-2.

Post-exposure prophylaxis (PEP)

Post exposure prophylaxis with TAF/TDF+FTC+RAL or TAF/TDF+FTC+DRV/c or DRV/r should be offered in case of high-risk contact with an ART-naive HIV-2 infected patient with detectable or undetermined VL. Alternatively, AZT+3TC could be used instead of TAF/TDF+FTC in combination with RAL or DVR/r.

In case of high-risk contacts with an ART-experienced HIV-2 infected patient with detectable or undetermined plasma viral load, 2 NRTIs plus a third agent (INI, DRV/r, boosted lopinavir (LPV/r) or boosted saquinavir (SQV/r) should be offered based on the history of previous ART regimens and treatment failures of the index patient, tolerability of the drugs, and on the results of genotypic resistance testing (reverse transcriptase, protease, and integrase), if available. Abacavir (ABC) should only be used with a verified negative HLA-B*5701 status.

Pre-exposure prophylaxis (PrEP)

PrEP is currently discussed and offered in HIV-1 settings. The sexual transmission of HIV-2 is roughly five times less efficient than the sexual transmission of HIV-1 [27, 28]. To date, there are no data available for the use and benefits of PrEP in HIV-2 settings**,** so that no reliable statement on this topic is currently possible.

Concluding remarks

There are only limited data on diagnostics, monitoring and treatment of HIV-2 infected patients and no European consensus guidelines for the management of these infections available.

State of art diagnostics enables the discrimination between HIV-1 and HIV-2, but diagnostics should remain mainly in hands of experienced or national reference laboratories. Commercial tests for HIV-1 RNA do not detect or quantify HIV-2 RNA. Recently, one commercial assay for detection and quantification of HIV-2 RNA has become available.

Antiretroviral therapy is challenging due to the limited number of HIV-2-effective drugs. Remarkably few data are available to assess the efficacy and safety of treatment regimens in pregnancy, infancy, and HIV-1/HIV-2 co-infections. Existing national guidelines and recommendations for HIV-2 ART are based mainly on expert experience, *in vitro* data, and extrapolation from HIV-1. Bioinformatics tools for interpretations of drug resistance and viral tropism are freely available.

There is still a need for additional and increased collaborations between clinicians and researchers from both developed countries and from HIV-2-endemic settings to fill all the existing gaps.

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Tables:

Table 1: Recommended drugs for first and second line treatment of HIV-2 infected

Backbone drugs (2 NRTIs)		**3rd drug**
TAF/TDF + FTC/3TC, or ABC + 3TC	**plus**	1 PI (DRV/r, DRV/c, LPV/r) or 1 INI (RAL, DTG*, EVG/c**), BIC ***)

3TC – lamivudine; ABC – abacavir; BIC – bictegravir, c – cobicistat; DRV/r – boosted darunavir; DTG – dolutegravir; EVG – elvitegravir; FTC – emtricitabine; LPV/r – boosted lopinavir; r – ritonavir; RAL – raltegravir; TAF – tenofovir alafenamide; TDF – tenofovir disoproxil fumarate.

*DTG: prescribers should consider the child bearing potential in women and pay attention to the current recommendations of medical agencies for drug safety

** EVG/r is not recommended for use during pregnancy because of substantially lower exposures of cobicistat and elvitegravir during the second and third trimesters.

***BIC is active against HIV-2 replication, but only in-vitro data are available (Smith 2018 [39]). BIC is recommended for the treatment of HIV-2, comparable to DTG (Gottlieb 2018 [1]). BIC is not evaluated in pregnant women and women of child bearing potential.

Table 2: HIV-2 resistance according to the HIV-2EU group resistance interpretation rule set [Charpentier, 2015; ref 10]; updated January 2020)

Drug	Mutations associated with high level of resistance	Mutations associated with intermediate level of resistance
AZT	• Q151M • S215A/C/F/L/Y + 1 of (N69S/T, K70R, Y115F, K223R)	• S215A/C/F/L/Y
3TC/FTC	• M184VI	• K65R
ABC	• K65R • Q151M • M184V/I + 1 of (L74V, Y115F)	• 2 of (D67N, K70R/N, M184V/I, S215A/C/F/L/Y)
TDF/TAF	• K65R • Q151M + V111I	
SQV	• G48V • L90M	• I84V
LPV	• V47A • I54M • 2 of (I82F, I84V, L90M)	• V62A + L99F • 1 of (I82F, I84V, L90M)
DRV	• I50V • I54M • I84V + L90M	• 1 of (I84V, L90M)

RAL	• N155H/R • Q148H/K/R • 1 of (E92Q, T97A) + Y143C/G/R • E92Q + T97A • 231ins (reference:[40])	• E92Q • Y143C/G/R
EVG	• E92Q/G • Q148H/K/R • N155H • T97A + Y143C • 231ins (reference:[40])	• Y143C
DTG	• G140S + Q148H/R • Q148K • E92Q + N155H • T97A + N155H • 231ins (reference:[40])	• E92Q • Q148H/R • N155H • T97A+ Y143C
BIC	• G140S + Q148H/R • Q148K • E92Q + N155H • T97A + N155H	• E92Q • Q148H/R • N155H • T97A+Y143C • 231ins (reference:[40])

Table 3: V3 loop amino acids positions features and CCR5/CRCX4 tropism [Döring, 2016; ref 35].

V3 Position	R5 feature	X4 feature	R5 weights	X4 weights
18	L	H,Q,F,M	0.69	-0.23, -0.15, -0.12, -0.1
19	I	R,K,V	0.19	-0.25, -0.23, -0.19
Insertion after position 22	-	H,Y	0.36	-0.18, -0.18
24	P	*NA*	0.17	*NA*
Insertion after position 24	-	I,V	0.45	-0.22, -0.21
23	Q	R	0.14	-0.14
27	Q	K	0.09	-0.12
13	T	R	0.11	-0.07
26	*NA*	N	*NA*	-0.09
10	A	K	0.09	-0.07
14	I	L	0.08	-0.08
22	S	*NA*	0.08	*NA*
15	A	G	0.08	-0.07
8	K	S	0.07	-0.07

The table shows discriminatory features of the geno2pheno$_{[coreceptor\text{-}hiv2]}$ model in the HIV-2 V3 loop that make up more than 75% of the total model weights. Positions of discriminatory features that were not described previously in the literature are shown in bold. The positions 18, 19, insertions after positions 24, and overall charge represent major genotypic markers according to Visseaux and colleagues [Visseaux, 2014; ref 37]. Entries marked with *NA* indicate features that did not exceed the 75% cut-off on the model weights.