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Antiretroviral Therapy for HIV-2 Infection in Non-Endemic Regions

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on behalf of the Spanish HIV-2 Network#

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Abstract

Human immunodeficiency virus type 2 (HIV-2) was isolated in AIDS patients in 1986. Around 1-2 million people are infected worldwide. The virus is less transmissible than HIV-1, being sexual contacts the most frequent route of acquisition. In the absence of antiretroviral therapy, most HIV-2 carriers will develop AIDS; however, it takes longer than in HIV-1 infection. There is no global pandemic caused by HIV-2, as the virus is largely confined to West Africa. Due to historical ties, HIV-2 is also prevalent in Portugal and its former colonies in Brazil, India, Mozambique, and Angola. Other European countries with hundreds to thousands of HIV-2 infections are France, Belgium, and Spain. A few hundred have been reported in North America, mostly in West African foreigners. Globally, HIV-2 infections are steadily declining. Although CD4 declines occur more slowly in HIV-2 than in HIV-1 patients, the CD4 recovery with antiretroviral treatment is smaller in the former. HIV-2 is naturally resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs) and some protease inhibitors. In contrast, HIV-2 is susceptible to all NRTIs and integrase inhibitors. Drug resistance in HIV-2 may develop earlier than in HIV-1 and select for mutations at distinct sites. Misdiagnosis of HIV-2 in patients wrongly considered as HIV-1 positive or in those dually infected may result in treatment failures with undetectable HIV-1RNA. Given the relatively large number of West Africans migrated to the European Union and North America, HIV-2 infection either alone or as coinfection with HIV-1 should be excluded at least once in all HIV-seroreactive persons. This should be stressed in the face of atypical HIV serological profiles, immunovirological disconnect (CD4 cell count loss despite undetectable HIV-1 viremia), and/or high epidemiological risks (birth in or sex partners from HIV-2 endemic regions). Superinfection with any HIV variant may occur in persons infected with the other, since there is no cross-protection. Thus, earlier antiretroviral therapy is warranted for either HIV-1 or HIV-2, given that it would protect from each other superinfection in persons at risk. **(AIDS Rev. 2020;22:44-56)**

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Key words

HIV-2. Antiretroviral therapy. Drug resistance. Integrase inhibitors. Dual HIV infection. HIV superinfection.

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Introduction

Human immunodeficiency virus type 2 (HIV-2) is a neglected virus despite estimates of 1-2 million people infected worldwide[1]. Progression to AIDS occurs in most HIV-2 carriers in the absence of antiretroviral therapy; however, it takes longer than in HIV-1-infected patients[2,3]. HIV-2 is less transmissible than HIV-1, being sexual contact the most frequent route of acquisition[4]. In contrast with HIV-1, there is no global pandemic caused by HIV-2, as the virus is largely confined to West Africa. Due to historical ties, HIV-2 is also prevalent in Portugal and its former colonies in Brazil, India, Mozambique, and Angola[5]. Other European countries with hundreds to thousands of HIV-2 infections are France, Belgium, and Spain[4,6,7]. A few hundred have been reported in North America, mostly in African foreigners[8]. Figure 1 graphically represents worldwide HIV-2 distribution. Whereas HIV-2 infections are steadily declining globally, migration flows are rising numbers in resource-rich countries[1,9].

Given the relatively large flux of West Africans that have moved and continue to migrate to the European Union and North America, HIV-2 positives are increasingly recognized outside endemic regions. Proper diagnosis and care of this population are warranted in western countries (Table 1). Therapeutic challenges may differ from those in HIV-2 endemic regions, where additional considerations must be taken into account and even be prioritized, including poor drug adherence, proper laboratory monitoring, ensuring drug supply, staff competence, etc[10].

Acute HIV-2 Infection

Less than five cases of acute HIV-2 infection have been reported so far in the literature[11-14]. One of the best described is a 69-year-old French male that developed a transient maculopapular skin rash, fatigue, and upper respiratory tract symptoms, following homosexual relationships with multiple sex partners[13]. Symptoms and signs reminded those seen in HIV-1 acute infections. However, the viral load peak was low (13,600 HIV-2 RNA copies/mL) in comparison with values observed in HIV-1 seroconverters, which generally are in the order of 10^5-10^6.

More recently, a report from Portugal described a 46-year-old male that experienced an unexplained rapid and severe CD4 count drop (up to a nadir of 89 cells/μL or 6%) following sexual intercourse with a casual partner while visiting Brazil[14]. Interestingly, he was known to be HIV-1 positive for 11 years and had undetectable plasma HIV-1 RNA under antiretroviral therapy (tenofovir, emtricitabine, and ritonavir-boosted atazanavir). He remained asymptomatic all time and antiretroviral therapy

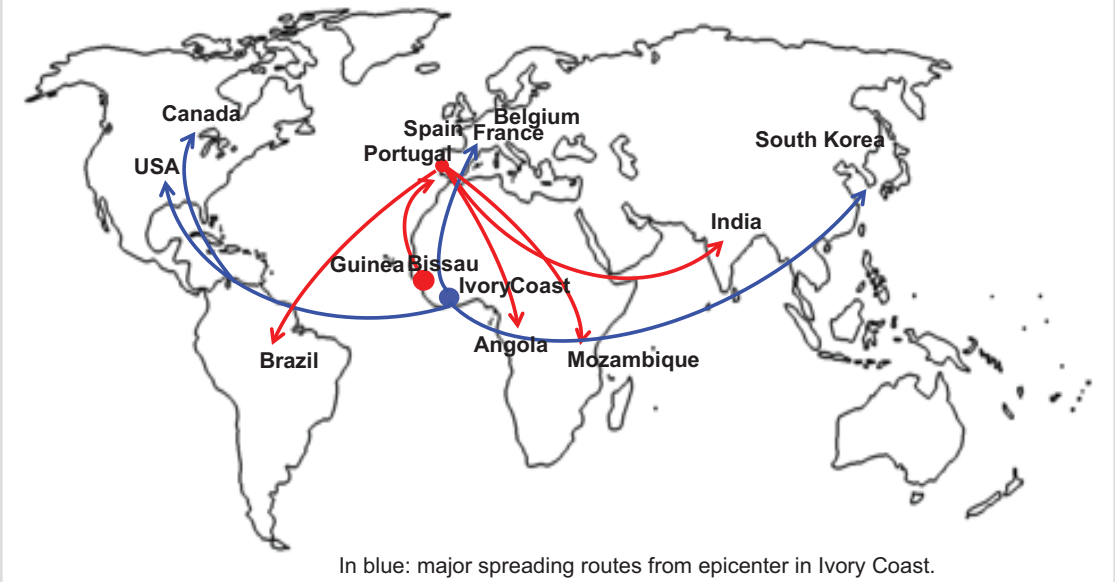

Figure 1. *Major routes of spreading of HIV-2 worldwide*[7].

Table 1. Major challenges in HIV-2 therapeutics in resource-rich countries

Missing primary HIV-2 infection, as it is generally asymptomatic or low symptomatic
Very slow decline of CD4+ T cells and of progression to AIDS
Difficulties in lab diagnosis, using either serology or nucleic acid testing
Some antiretrovirals are not active, including NNRTIs and some PIs
Slow and poor CD4 recovery in response to antiretroviral therapy
More frequent selection of drug resistance and multidrug resistance
Uncertainty on simplification strategies. No chance for combo DTG-RPV and no data on DTG-3TC
PrEP will work
Pregnant women should be treated before delivery
Dual HIV-1/HIV-2 infections must be confirmed and treated with triple regimens including integrase inhibitors or darunavir
HIV superinfection may occur in untreated persons engaged in risk practices
Antiretroviral therapy should be prescribed as soon as possible in HIV-2 persons

NNRTIs: non-nucleoside reverse transcriptase inhibitors; PrEP: pre-exposure prophylaxis; PIs: protease inhibitors; DTG: dolutegravir; RPV: rilpivirine; 3TC: lamivudine.

was not modified. Three years later, the HIV-1/HIV-2 discrimination test was repeated. This time it was positive for antibodies against both viruses. Plasma HIV-2 RNA was 5320 copies/μL. Genotypic resistance showed drug resistance mutations at the PR, RT, and IN genes. This case highlights the unfortunate low clinical suspicion for HIV-2 in western countries.

HIV-2 Natural History and Clinical Manifestations

Overall, HIV-2 infection progress slowly to AIDS, with an estimated average of 15-20 years in the absence of antiretroviral therapy[2,3]. This milder pathogenicity of HIV-2 compared to HIV-1 biologically correlates with long-lasting periods of lower viral load and higher CD4 cell counts[15], even during primary HIV-2 infection[12].

In a cohort from Senegal, 44% of HIV-2 persons had baseline undetectable viremia[15]. This rate was 70% in the French cohort[4] but 40% in the Spanish cohort[7]. Differences in the rate of untreated, aviremic HIV-2 persons may be due to distinct rates of people presenting with advanced disease (CD4 counts below 200 cells/μL and/or AIDS-defining illnesses). Overall, nearly 10% of HIV-2 persons behave as long-term non-progressors, meaning that they depict undetectable viremia for longer than 10 years in the absence of antiretroviral therapy[16].

Once CD4 counts drop below 200 cells/μL in HIV-2 patients, the incidence and spectrum of opportunistic infections as well as the mortality rate do not seem to differ much from HIV-1 infection[17,18]. However, as expected, the geographic origin and place of living of most HIV-2 persons, namely, West Africa, predispose more frequently to certain clinical conditions, such as tuberculosis, toxoplasmosis, and bacterial diarrhea.

Access to antiretrovirals is increasing across low-income countries, including many regions in West Africa where HIV-2 is endemic. However, unique challenges remain, including low adherence, lack of medication supply, drug resistance, staff competence, and difficult access to laboratory monitoring[10]. Whereas these obstacles are overcome in western countries, earlier observations have highlighted a poorer response to antiretroviral therapy in HIV-2 compared to HIV-1 patients, with lower viral suppression rates and impaired CD4 T cell count recovery[6,19-21].

HIV-2 treatment indication and monitoring is often problematic in low-income endemic countries, given that access to CD4 counts is difficult, and measuring plasma HIV-2 RNA is rarely available[10]. Although no studies have specifically examined when to start antiretroviral therapy in HIV-2 individuals, given the slow disease progression, difficulties in access to medications and the threat of lifelong medication adherence and side effects, some guidelines, i.e., the British, just recommended treatment to HIV-2 individuals with evidence of immunosuppression, such as those with CD4 counts <500 cells/μL[22]. Further deferral of treatment could be harmful since immune recovery is both slower and poorer in patients with HIV-2 versus HIV-1[21], which may be more relevant when therapy is initiated with deep immunodeficiency[23]. In the large European observational ACHIEVE-COHERE collaboration, CD4 gains at 12 months of beginning first-line antiretroviral therapy were 75 cells/mm^3 greater in HIV-1 (n = 49,455) than in HIV-2 patients (n = 198). The difference remained significant after adjusting for baseline viremia, treatment regimen, and baseline CD4 count[21].

Although a large proportion of individuals infected with HIV-2 may remain aviremic for years, a subset showed CD4+ T cells with markers of elevated activation and other pathological characteristics, thereby increasing the risk of AIDS and non-AIDS related illnesses[23]. This observation could explain, at least partially, the poor immunologic recovery of CD4 counts in HIV-2 under antiretroviral therapy compared to HIV-1 in distinct observational studies, including a few conducted in Africa[24,25]. Therefore, when possible initiation of antiretroviral therapy in HIV-2-infected patients should be advanced and be given as soon as possible, following what is currently recommended for HIV-1 infection. This advice is currently recommended at the latest DHHS guidelines[26]. The major caveat for HIV-2 could be the limited current armamentarium in the face of lifelong treatment.

Table 2. Main features of new HIV-2 diagnoses in the USA and Spain

	USA (2010-2017)[8]	Spain (2010-2019)
Number	196	172
Male gender (%)	51	63
Mean age (years-old)	49	42
Transmission route (%)		
Heterosexual	61	80
Homosexual men	25	4
Birth in endemic countries (%)	45	80
Dual HIV-1 plus HIV-2 coinfection (%)	6	10

HIV-1: Human immunodeficiency virus type 1, HIV-2: Human immunodeficiency virus type 2.

HIV-2 Diagnosis

Given antigenic similarities between HIV-1 and HIV-2, serological cross-reactivity between respective antibodies appears using screening assays. However, differences mostly for envelope proteins allow specific antibody discrimination. In the United States, since 2014, a new testing algorithm aimed to distinguish HIV-1 and HIV-2 was implemented, recommending a supplemental differentiation test in all initially reactive HIV specimens[27]. When HIV-2 seroreactivity appears, either alone or along with HIV-1, a specific nucleic acid test for HIV-2 is warranted for further confirmation.

In the USA, a total of 166 cases of HIV-2 had been reported until 2009, being the first case diagnosed in 1987[28]. During the period 2010-2017, another 198 HIV-2 cases had been identified from a total of 327,700 new HIV diagnoses (overall rate 6 per 10,000)[8]. Since the implementation in 2014 of the new HIV diagnostic algorithm, the yearly number of new HIV-2 diagnoses has ranged from 25 to 35. There is a similar gender distribution. Compared to HIV-1, new diagnoses of HIV-2 tend to be older. Indeed, 57% of new HIV-2 cases are older than 45 years old. Overall, 74% are black. Heterosexual transmission is the most likely route of infection (61%), being only 25% of homosexual men. Vertical HIV-2 cases have not been reported to date. Up to 45% of HIV-2 new diagnoses have been made in persons born in countries where HIV-2 is endemic. Dual HIV-1 plus HIV-2 infection was found in 11 (6%). Finally, 55% of new cases are concentrated in the northeast states (Table 2).

At the European Union, Spain has a nationwide HIV-2 register since 1989[7]. Up to December 2019, a total of 393 cases had been reported. Male (63%) predominate over female (35%). The mean age at diagnosis was 42 years old. Overall 76% are sub-Saharan Africans, whereas 14% are native Spaniards. Dual HIV-1 and HIV-2 coinfection was found in 38 (10%). Heterosexual contact was the most likely route of HIV-2 acquisition, being homosexual men only 4%. Roughly one-third presented with CD4 counts below 200 cells/µl and/or AIDS clinical events. Plasma HIV-2 RNA was undetectable at baseline in 40% of patients (Table 3). To date, half of the HIV-2 carriers have received antiretroviral therapy, using integrase inhibitors (INIs) 48 individuals[29]. New diagnoses of HIV-2 in Spain have remained stable, since 2010, with an average of 20 cases yearly (Fig. 2). Illegal immigration from Northwest African borders accounts for over 80% of new HIV-2 diagnoses in Spain. Most cases are concentrated in the largest urban areas and in the Mediterranean coasts (Fig. 3).

Given the relatively large number of West Africans steadily moving to the European Union and North America, HIV-2 infection either alone or as coinfection with HIV-1 should be excluded at least once in all HIV-seroreactive persons, especially when showing atypical HIV serological profiles, immunovirological disconnect (CD4 cell count loss despite undetectable HIV-1 viremia), and/or high epidemiological risks (birth in or sex partners from HIV-2 endemic regions)[7].

Table 3. Main features of HIV-2 reported cases in Spain

Characteristics	n (%)
Total	393
Gender	
Female	139 (35.3)
Male	249 (63.3)
Unknown	5 (1.4)
Median age (years) (range)	42 (0-83)
Country/region of origin	
Sub-Saharan Africa	300 (76.3)
Portugal	10 (2.5)
Spain	55 (14.0)
Latin America	7 (1.5)
Others*	4 (1.1)
Unknown	17 (4.3)
Most likely transmission route	
Heterosexual	254 (64.6)
Homosexual	15 (3.8)
Injection drug use	7 (1.8)
Transfusions	2 (0.9)
Mother-to-child	2 (0.6)
Unknown	111 (28.2)
HIV-1 coinfection	37 (10)
HIV-2 variant**	
Group A	113 (88.1)
Group B	18 (11.9)

*France, India, and Morocco (2), **HIV-2 subtyping could not be done in the rest mostly due to low or undetectable viremia.

Initial Treatment of HIV-2 Infection

HIV-2 is generally not or just poorly addressed in most antiretroviral treatment guidelines. There have been no randomized trials addressing the question of when to start antiretroviral therapy in HIV-2 infection or the preferred choice for initial or second-line therapy. In the United States, the 2019 updated DHHS guidelines did not recommend any specific treatment regimen for HIV-2 infection, although it specified which drugs should not be used[26]. The World Health Organization recommends dolutegravir-containing regimens as the preferred first-line regimen for people living with HIV regardless of HIV type[30]. The European AIDS Clinical Society neither advice nor mention antiretroviral treatment for HIV-2 individuals[31]. The latest recommendation on HIV-2 therapy by the British HIV Association was published in 2010[22]. An updated version is expected to be released soon.

The optimal treatment strategies for HIV-2 remain to be well defined. Questions on when to initiate treatment and which drugs to use are unknown. However, three clinical trials are currently underway to address these critical questions. FIT-2 (First-line Treatment for HIV-2; NCT02150993) is being conducted in West Africa, testing the efficacy and safety of distinct first-line triple options (tenofovir vs. zidovudine, lamivudine vs. emtricitabine, and plus lopinavir/r vs. raltegravir). Another two trials (NCT01605890 and NCT 02180438) are evaluating the efficacy of raltegravir and elvitegravir/cobicistat, respectively, in HIV-2 patients.

Following the rationale applied to HIV-1 infection, most experts would support beginning antiretroviral therapy earlier in HIV-2 patients, before CD4 counts go down 350-500 cells/μL. Nevertheless, questions remain given that there are fewer therapeutic options. Furthermore, treatment as prevention (TasP) of HIV-2 sexual transmission is not as clear as for HIV-1 infection, since HIV-2 plasma viremia is often undetectable. Finally, concerns exist on poor drug adherence, adequate laboratory monitoring, and proper drug supply[10].

Most HIV-2 treatment recommendations have been done according to the information recorded from observational cohorts and from drug susceptibility experiments in viral cultures. In a retrospective observational multicenter European study, a scheme based on two nucleos(t)ide analogs plus either another nucleoside polymerase inhibitor or a protease inhibitor (PI), demonstrated that regimens including PIs outperformed triple nucleoside combinations[32]. However, as a matter of fact, and following the HIV-1 path, INIs have become the preferred third agents in combination with a two nucleos(t)ide backbone as first-line HIV-2 therapy[29,33-35].

In summary, all antiretrovirals currently available to treat HIV-2 patients are taken from the HIV-1 armamentarium, being some of them inactive or just depicting a residual antiviral effect, which limits substantially therapeutic options for HIV-2 patients. More specific and stronger antivirals are needed for the growing subset of HIV-2-infected individuals progressing to advanced immunodeficiency, most of who already have failed and selected resistance to older antiretrovirals[34,36-39].

HIV-2 Treatment Failures

Virological suppression after beginning antiretroviral therapy tends to occur less frequently and less rapidly in HIV-2 than in HIV-1 patients[35,40]. Although an intrinsic lower activity of some antiretrovirals and lower resistance barriers may contribute to this observation, other reasons may account for it, including poorer drug adherence, especially in resource-poor regions[10].

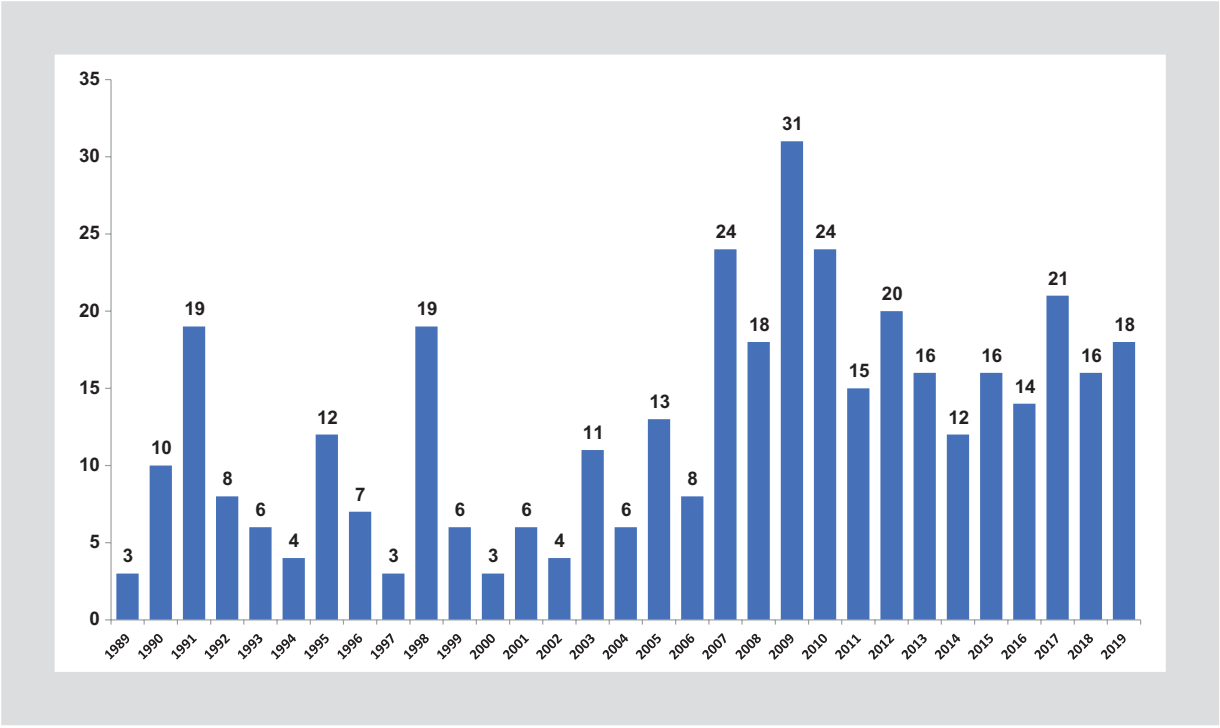

Figure 2. *HIV-2 incidence in Spain.*

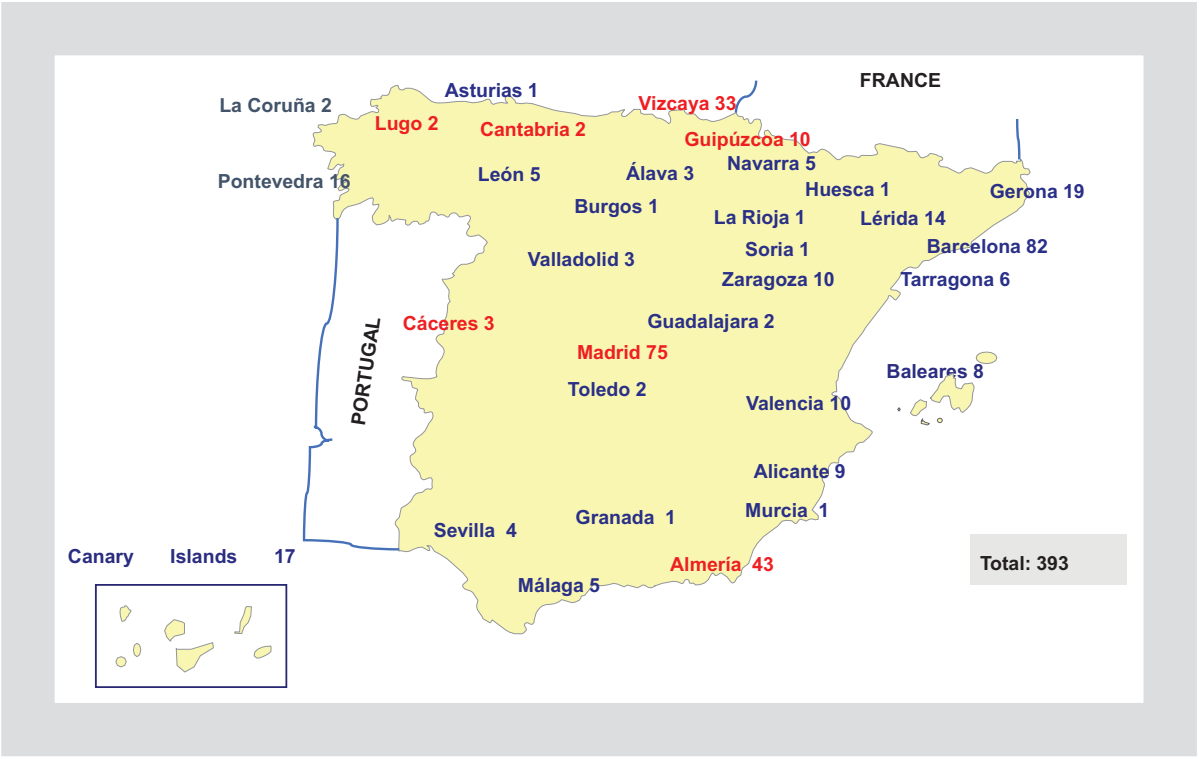

Figure 3. *Geographic distribution of HIV-2 cases reported in Spain.*

Table 4. HIV-2 resistance mutations[52]

	Study population			TSMs	
	ARV-naive	ARV-experienced	Total	Polymorphic	Nonpolymorphic
PR	483	232	16	4 (V10I, I64V, V71I, **L99F**)	12 (V33I, K45R, V47A, I50V, I54M, **T56V**, V62A, A73G, I82F, I84V, F85L, L90M)
RT	333	252	12	3 (N69S, V111I, F214L)	9 (**K40R**, A62V, K65R, K70R, Y115F, Q151M, M184I, M184V, S215Y)
IN	236	60	14	3 (**I84V, A119T**, **V141I**)	11 (**Q91R**, E92A, E92Q, E97A, G140S, Y143G, Q148R, A153G, N155H, **H156R**, **R231 insert**)

*All published HIV-2 pol sequences were analyzed. Overall 90% belonged to HIV-2 Group A and 8% to Group B. RT: reverse transcriptase, PR: protease, IN: integrase, ARV: antiretroviral, TSMs: treatment-selected mutations.

Selection of multi-class resistance on the first-line failure and the limited therapeutic armamentarium for rescue interventions make HIV-2 treatment failure a major challenge. Considerations of salvage therapy must be guided by expertise and laboratory support. Several genotypic resistance algorithms are freely available online to help building rescue interventions in patients experiencing virological treatment failure: (i) HIV-2EU HIV-GRADE internet tool[41]; German HIV-2 drug resistance analyses (http://www.hiv-grade.de); (ii) Rega algorithm (http://regaweb.med.kuleuven.be/software/rega_algorithm); and (iii) Stanford HIV drug resistance database (http://www.hivdb.stanford.edu).

HIV-2 Drug Resistance

In vitro susceptibility studies have reported differences in the activity of several antiretrovirals against HIV-2 compared to HIV-1[42]. First, HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors (NNRTI) by virtue of multiple naturally occurring amino acid differences between each virus at the hydrophobic pocket that binds NNRTIs[43]. Second, the mechanism of AZT resistance differs between HIV-1 and HIV-2. While HIV-1 resistance to AZT is usually caused by pyrophosphorolysis-mediated primer unblocking, the thymidine analog mutations responsible for this process develop less frequently in HIV-2 under AZT selection pressure[44]. The absence of primer unblocking in HIV-2 is partially explained by differences between HIV-1 and HIV-2 at amino acids 67-75 involved in pyrophosphorolysis[44,45]. Third, differences in the HIV-1 and HIV-2 protease substrate cleft amino acids are responsible for the reduced activity of several PIs against HIV-2[46,47].

Most mutations that develop in HIV-2 during therapy with NRTIs, PIs, and INIs occur at the same HIV-1 drug resistance positions. Exceptions include V111I in RT[6,48,49], L99F in PR[36,50], and an insertion at position 231 in IN[51]. A recent meta-analysis led by the Stanford's team along with French and Spanish experts has provided the first comprehensive list of PR, RT, and IN mutations in ARV-naïve and treated persons using published sequences[52]. There are 42 HIV-2 drug resistance mutations, including nine novel identified changes (Table 4). Despite the much lower number of HIV-2 sequences compared with the number of HIV-1 sequences, 16 mutations in PR, 12 mutations in RT, and 14 mutations in IN are selected by ARV therapy. These numbers will likely increase as more data become available, including information from HIV-2 groups other than A, to which belong roughly 90% of HIV-2 sequences published up to date.

Transmission of drug-resistant viruses has never been a big concern for HIV-2, given that wide use of antiretrovirals has not occurred yet in most West African endemic regions, and because antiretroviral therapy has often been delayed for HIV-2 patients. However, data from western countries, such as France, Belgium, or Luxembourg, suggest that transmitted drug resistance may occur in HIV-2 as in HIV-1[6,53].

Antiretroviral Simplification in HIV-2 Infection

Although triple-drug combination therapy remains the standard treatment for HIV-1 infection, attempts for moving to simplified regimens using two drugs have succeeded in patients that had achieved and sustained undetectable viremia for a while under triple-drug regimens[54]. Combinations of dolutegravir plus rilpivirine are nowadays widely used in HIV-1 patients without prior history of treatment failure and selection of drug-resistant viruses. On the other hand, long-acting formulations of antiretrovirals such as cabotegravir and rilpivirine will

most likely be approved soon[55]. In all these situations, unintentional exposure to INI monotherapy will occur in patients infected with HIV-2, since rilpivirine is not active. Therefore, particular caution for excluding HIV-2 is warranted when planning treatment simplification with rilpivirine on board. This alert resembles that to exclude hepatitis B coinfection before removing tenofovir as part of prior triple-drug regimens. In our knowledge, data using dolutegravir plus lamivudine as treatment simplification for HIV-2 are not available, but it seems reasonable to assume that it would work as for HIV-1 infection.

Activity of Latest and Next coming Antiretrovirals for HIV-2

Several new antiretrovirals belonging to classical drug families or new ones are in the final steps of clinical development and could be of interest as HIV-2 therapy. Within entry inhibitors, fostemsavir is a CD4 attachment inhibitor that binds to gp120[56]. Since the HIV-2 envelope glycoprotein gp105 is antigenically different, no cross-activity should be expected against HIV-2.

Ibalizumab is a humanized monoclonal antibody that acts as a post-attachment inhibitor by binding CD4 on T lymphocytes and preventing HIV interaction with co-receptors CCR5 or CXCR4[57]. It has already been approved by the FDA as a new intravenous antiretroviral agent for heavily treated HIV+ adults with multidrug-resistant viruses. Although data on the activity of ibalizumab on HIV-2 are scarce, the drug should be expected to exert inhibitory activity against HIV-2.

After several drawbacks, there are currently trials moving ahead, testing HIV-1 maturation inhibitors. These agents are small-molecule compounds that block a late step in the viral protease-mediated processing of the gag polyprotein precursor, which is responsible for the formation of virus particles. Bevirimat is highly effective in blocking HIV-1 replication, but its activity is compromised by naturally occurring polymorphisms within gag. Recent bevirimat analogs, referred to as "second-generation" maturation inhibitors, have been designed to overcome this issue[58]. These agents bind to HIV polyproteins before PIs act. No data have been released regarding their potential activity against HIV-2, but no activity is expected given the high specificity of their blocking mechanism.

Cabotegravir is a dolutegravir analog with a longer half-life and potential intramuscular monthly use[59]. This drug is a promising agent against HIV-2. Bictegravir is a newly unboosted INI given once daily[60]; it would be also active against HIV-2.

Table 5. Antiviral effect of the newest antiretrovirals against HIV-2

Class	Drug	HIV-2 activity
Nucleos(t)ide analogs	Tenofovir alafenamide	Yes
	Islatravir	Yes
Non-nucleoside analogs	Rilpivirine	No
	Doravirine	No
Protease inhibitors	Darunavir	Yes
Integrase inhibitors	Dolutegravir	Yes
	Bictegravir	Yes
	Cabotegravir	Yes
Entry inhibitors	Fostemsavir	No
	Ibalizumab	Yes
Maturation inhibitors	Bevirimat	No

Doravirine is a new non-nucleoside polymerase inhibitor that depicts activity against classical HIV-1 variants resistant to other non-nucleosides[61]. Furthermore, the drug has been designed to overcome the classical neuro/cardiotoxicity of other agents within this family. However, given its allosteric mechanism of inhibition, outside the polymerase active site, no activity of doravirine is expected against HIV-2.

Islatravir is a novel, first-in-class nucleoside reverse transcriptase translocation inhibitor that depicts potent antiviral activity along with a unique resistance profile[62]. No data exist on its inhibitory effect on HIV 2, but it most likely will work given its mechanism of action[63].

Preliminary data suggest that the production of nanoformulated prodrugs of some antiretroviral molecules might allow medications to be administered on a yearly basis, as recently shown for cabotegravir derivates[64]. Although no data have been produced so far for HIV-2 using very long-acting antiretrovirals, it would be expected that many results obtained testing HIV-1 would apply to HIV-2[65]. The advent of these new formulations could have a great impact in resource-poor regions, where drug adherence and medication supply are often a challenge.

Table 5 summarizes the expected activity against HIV-2 of the newest antiretroviral agents recently approved or at the latest steps of clinical development.

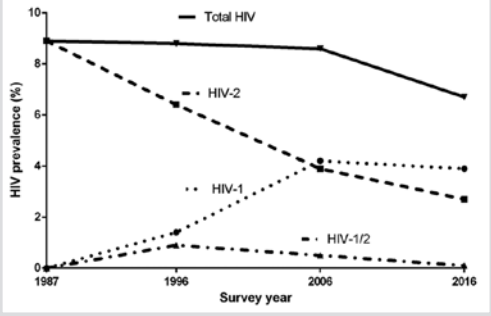

Figure 4. *Trends in HIV prevalence in Bissau*[76].

Pre-exposure Prophylaxis (PrEP) and HIV-2

The success of antiretroviral therapy during the past 25 years has led to steadily expand its use to all HIV-1 carriers and even include those uninfected at risk. Nowadays, antiretroviral therapy is recommended to all HIV-infected individuals without a CD4 cell count restriction (Fig. 4). Moreover, it should be given as early as possible following diagnosis, a strategy known as the rapid initiation of antiretroviral therapy[66]. Earlier treatment interventions are associated with benefits for both patients and society, as transmissions do not occur from viral suppressed patients. This effect is known as TasP. More recently, the benefits of prescribing antiretrovirals to uninfected individuals engaged in high-risk behaviors have expanded treatment beyond patients, a strategy is known as PrEP[67].

Data on either TasP or PrEP are rather scarce for HIV-2 infection, but the same rationale than for HIV-1 would be applicable. However, some considerations merit attention. Nearly half of HIV-2 carriers may harbor undetectable plasma viremia at presentation, reflecting spontaneous very low viral replication in the absence of any antiretroviral therapy[68-70]. It would be worth exposing this subset of patients to lifelong drugs and their side effects? Furthermore, the psychological burden and potential stigma derived from daily HIV medications would not be negligible. Finally, what about HIV-2 aviremic individuals that deny sexual partners or other risk behaviors: should they be treated anyway? Should condoms be enough if they have sex partners?

Another caveat for PrEP is for sex partners of HIV-2 carriers. Currently approved medications to prevent HIV-1 acquisition, namely, tenofovir plus emtricitabine, are also active to prevent HIV-2 transmission. Thus, the same drugs will protect from infection in persons engaged in high-risk behaviors regardless of HIV variant exposure. This would the case for prostitutes or persons with non-commercial multiple sex partners.

Pregnancy in HIV-2 Mothers

Vertical transmission of HIV-2 has been well demonstrated, although perinatal HIV-2 infection to newborns occurs less frequently than from HIV-1 mothers[71]. The overall lower viremia in HIV-2 compared to HIV-1 mothers largely accounts for it. Given that undetectable viral load at the time of delivery would halt vertical transmissions, all HIV-2 mothers should receive antiretroviral therapy before giving birth. Thereafter they should be advised against breastfeeding. Once antiretroviral therapy has been initiated in pregnant women, it would be worth to keep them on and consider discontinuation only in the face of major obstacles.

Dual HIV-1 and HIV-2 Coinfection

Given that HIV infection does not elicit protective immunity, superinfection with HIV-1 in persons carrying HIV-2, or vice versa, may occur in places where both viruses cocirculate[25,72-74]. HIV-2 has circulated for decades in West Africa with relatively high endemicity in some regions, such as Guinea-Bissau and Ivory Coast[75,76]. Once HIV-1 entered the region and begun spreading more efficiently than HIV-2, the occurrence of dual HIV-1 and HIV-2 infections was the expected auspicious scenario[76,77]. Indeed, the first dually infected individual was reported in Ivory Coast in 1988[72]. However, data from Bissau have shown that once HIV-1 entered the region, it tended to predominate keeping dual infections as only marginal, below 5-10% (Fig. 5)[76].

In Spain, the first confirmed case of dual HIV-1 plus HIV-2 coinfection was reported in 1993[78]. To date, a total of 37 cases (10%) of dual infection out of 393 total number of HIV-2 cases have been accumulated[79]. In agreement with prior studies conducted in West Africa[25,80], dually infected patients in Spain were younger and had lower CD4 counts than HIV-2 monoinfected persons. Thus, antiretroviral therapy should not be deferred in this population and attention to include drugs active against both viruses should be ensured to minimize the risk of viral escape[81,82]. Furthermore, viral load monitoring should be mandatory for both HIV-1 and HIV-2 patients undergoing antiretroviral therapy.

In our series, up to 80% of dually infected patients treated achieved viral suppression for HIV-2, a rate

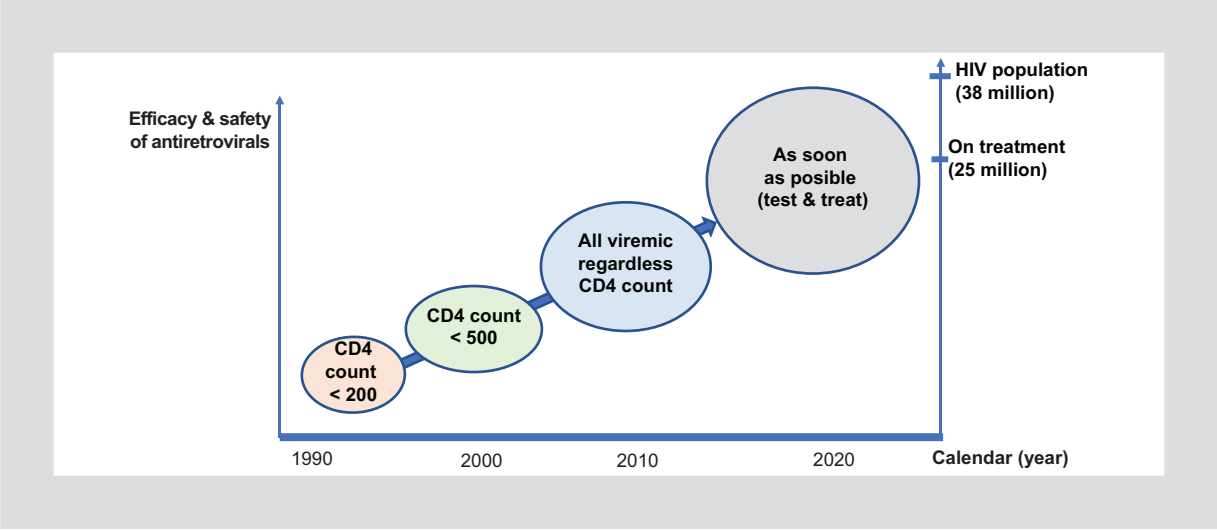

Figure 5. *Trends in the prescription of antiretroviral therapy.*

similar to the 85% seen for HIV-1. Three out of the four HIV-2 virologic failures occurred in patients treated with optimal regimens, including two nucleoside analogs plus one PI (two) and one unique individual with CD4 counts below 100 cells/μL, despite being treated with nucleoside analogs, and PIs plus raltegravir. The remaining HIV-2 failure corresponded to one person back to 2007 treated with two nucleoside analogs plus fosamprenavir who failed to suppress both viruses[79].

Overall, the proportion of patients who successfully controlled HIV-1 and HIV-2 in our series was greater than in prior reports, in which inadvertently some individuals received NNRTI[25,74,75]. Likewise, the CD4 count gain of our dual coinfected patients was satisfactory (median increase of 212 cells/μL). It should be noted that most patients in our series received HIV-2 active PIs and/or INIs, whose antiviral activity has been well documented[83]. In our knowledge, this was the first report showing the efficacy of INIs in a small series of HIV-1/HIV-2 dually coinfected patients. A report from 2009 just described one coinfected individual treated with raltegravir plus nucleoside analogs that experienced a favorable treatment response[19].

Clinical suspicion of dual HIV-1 plus HIV-2 coinfection should especially be considered for seropositive West African natives, people have traveled to (or lived in) HIV-2 endemic regions acknowledging risk behaviors, and anyone with sexual partners from West Africa. Confirmation is required for presumably dual infections, as unique considerations for antiretroviral therapy exist for this population[81-84]. Demonstration of RNA and/or proviral DNA for both HIV-1 and HIV-2 constitutes the most definitive evidence of dual infection, although discriminatory serological tests may be helpful as well.

Drugs exhibiting activity against HIV-2 should be ensured in any antiretroviral combination chosen to treat dually infected patients. All integrase strand transfer inhibitors, most nucleos(t)ide reverse transcriptase inhibitors, and some PIs, such as darunavir or lopinavir depict activity against HIV-2[21]. However, frequent selection of HIV-2-resistant variants along with slower immune restoration is relatively common when treating HIV-2 patients[83].

HIV Superinfection

The protective effect of HIV-2 against HIV-1 infection was reported in one cohort in Senegal in 1995[85] but was not replicated in other studies[86,87]. A more recent study on a cohort in Guinea-Bissau suggested that HIV-2 may have an inhibitory effect on the rate of HIV-1 disease progression[88]. However, the natural history and long-term prognosis of dually infected patients remains poorly understood.

The potential protective effect of ART in preventing the acquisition of HIV-1 should be considered when deciding whether treatment should be initiated in patients with HIV-2 mono-infection. Indeed, the latest DHHS guidelines suggest that ART should be started at or soon after HIV-2 diagnosis[26].

Four cases of superinfection have been reported in the literature. Whereas one individual experienced HIV-2 superinfection after longstanding HIV-1 infection[14], another three acquired HIV-1 after carrying

HIV-2 for years[79,89,90]. The Spanish case was a native female sex worker with long-lasting known and asymptomatic HIV-2 infection that experienced HIV-1 superinfection whereas she continued having sexual risky behaviors[79]. The case underlined the need for repeated testing and excluding HIV-1 periodically in the subset of HIV-2 carriers that continue having sexual risky behaviors in the absence of antiretroviral therapy.

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#Spanish HIV-2 Network

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