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CHAPTER 56

Epidemiology, Natural History and Treatment of HIV-2 Infections

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Introduction

In 1986, 3 years after the discovery of HIV-1, another retrovirus was identified, and named HIV-2.[1,2] It was isolated from West African patients with AIDS and its discovery caused concern that another devastating epidemic was at hand. Quite soon, it was shown that HIV-2 is less transmissible, is characterized by slower disease progression, and is geographically limited to West Africa and countries with direct ties to that region. The probable explanation of the epidemiological differences is that the plasma viral load in HIV-2 infected persons tends to be much lower than in HIV-1 infected persons.[3–6] In this chapter, the epidemiology, natural history, interactions with HIV-1, and treatment of HIV-2 are discussed. The comparison with HIV-1 is central to this chapter (see Table 56.1).[3–32]

Epidemiology

The transmission routes of HIV-2 are the same as for HIV-1: vaginal intercourse, anal intercourse, mother-to-child transmission, blood transfusion, parenteral (e.g. needle-stick incidents, needle sharing among intravenous drug users).[7] The efficiency of heterosexual transmission of HIV-2 is about $^1/_3$–$^1/_4$ that of HIV-1.[33,8] This can be explained by the generally lower plasma viral load, but no data have been published to prove this. Heterosexual intercourse is thought to account for the large majority of HIV-2 infections worldwide.

Prevalence and Incidence

The prevalence of HIV-2 exceeds 5% in the adult general population in only one country, Guinea-Bissau.[34] In other West African countries the prevalence in the general population is usually around 1 or 2%. Among high-risk groups higher prevalences have been observed (e.g. among female commercial sex workers: 38% in Southern Senegal,[35] 27.5% in The Gambia,[36] 41% in Abidjan, Cote d'Ivoire).[37] Outside West Africa, the infection is found in Portugal (the former colonial power in Guinea-Bissau), where 4% of AIDS cases are caused by HIV-2, and sporadically elsewhere in Europe.[38–41] In the USA, only one case of HIV-2 infection was detected among 7 000 000 blood donors over a 4-year period (1997–2000).[42] Sporadic cases of HIV-2 have also been detected in Asia (e.g. India, Korea) and South America (e.g. Brazil).

All repeated cross-sectional studies from West African countries have shown stable or declining prevalences of HIV-2; this was the case in diverse populations like female commercial sex workers,[33,36,37,43–46] an occupational cohort,[34] pregnant women,[34,37,47–49] STD patients,[50,51,51A] and the general population.[52]

There are very few studies reporting incidence rates of HIV-2. In a peri-urban community in Guinea-Bissau the incidence was 0.5 per 100 person-years of observation (pyo);[53] among female commercial sex workers in Dakar the incidence rate was 1.1 per 100 pyo.[33] Three cohort studies reported incidence rates over different time periods; among commercial sex workers in Dakar the incidence was stable[33] and in an occupational cohort and in a peri-urban

Table 56.1 Comparing HIV-1 and HIV-2

Characteristic	HIV-1	HIV-2
Epidemiological		
Geographic spread[7]	Worldwide	West Africa; rare elsewhere
Risk factors[7]	History of STDs, laboratory evidence of STIs, multiple partners, history of commercial sex	Same
Age with highest prevalence	20–34 years	40–55 years
Epidemic trend	Variable	Stable or declining in most countries
Global number of cases[7]	40 000 000	2 000 000[a]
Transmission routes[7]	Heterosexual, homosexual, mother-to-child, blood transfusions, needle sharing/ incidents	Same
Mother-to-child-transmission[4]	20–40%	1–4%
Sexual transmission[8]		$^1/_3$–$^1/_4$ of that of HIV-1
Clinical		
Median time to progression to AIDS[5,6,22]	10 years	>10 years
Kaposi's Sarcoma[17]	Common	Less common
Proportion of infected subjects that develop AIDS if not treated	>99%	Unknown, but much lower
Independent predictors of AIDS and mortality[5,6,15]	High PVL and low CD4	High PVL and low CD4
Excess mortality (compared with uninfected adults)[18]	10-fold	2–3 fold
Virological		
Closest simian virus	SIV_{cpz}	SIV_{sm}
Homology to closest simian virus	Distant	75–85%
Presumed timing of zoonotic event[12]	1930	1940
Presumed number of zoonotic events	1 (causing worldwide HIV-1 group M epidemic) several (causing sporadic N and M infections)	8 (equal to number of subtypes)
Subtypes[9,10,11,23]	Within group M: A,B,C,D,F, G,H, I,J,K, and several circulating recombinant forms	A,B,C,D,E,F,G,H
Genes	*pol*, *gag*, *env*, *nef*, *tat*, *rev*, *vif*, *vpr*	Same
	vpu	*vpx*
Plasma viral load[3,5,14,19]	Usually high: 10 000–100 000 copies/ml	Usually low: undetectable to 1000 copies/ml; $^1/_3$–$^1/_5$ of subjects have undetectable PVL
Proviral load (in asymptomatic subjects)[13,14,16,24,25]	Similar	Similar
Use of co-receptors[21]	CCR5 and CXCR4	Broader: CCR5 and CXCR4 and several others
Sensitive to NNRTI[20]	Yes	No
Immunological		
CD4 decline[14,26]	Fast	Slow
Immune activation[27,28]	High	Low
Neutralizing antibodies	Efficient, broad specificity	Less efficient, narrow specificity
CTL[29,30,31]	Common, mostly against *gag*	Same
Apoptosis of T cells[27,32]	High	Low
Cross-reactive responses to other HIV[29]	46% of patients have CTL responses to HIV-2 peptides	27% of patients have CTL responses to HIV-1 peptides

STD, sexually transmitted disease; STI, sexually transmitted infection; PVL, plasma viral load; SIV, simian immunodeficiency virus; cpz, chimpanzee; sm, sooty mangabey; CTL, cytotoxic T lymphocyte; NNRTI, non-nucleoside reverse transcriptase inhibitor; PBMC, peripheral blood mononuclear cell. [a]Author's estimate.

community in Bissau the rates were falling over time in men and stable in women.[34,52] Because all studies report stable or declining incidences and prevalences in West Africa, and no new HIV-2 epidemics have been observed outside West Africa, HIV-2 should not be considered an emergent epidemic, but an epidemic in decline.

In striking contrast to HIV-1, the highest prevalence of HIV-2 is not observed in young adults (15 to 34 years) but in older adults. This is the case in all study populations, whether female commercial sex workers, clinic patients, pregnant women or the general population. HIV-2 infection is very rare in children, even in Guinea-Bissau. The higher prevalence among older people could be the result of a cohort effect (lifelong infection with low mortality), or of an increased susceptibility of older persons, especially women.[54,55] The low prevalence among children is due to the very low mother-to-child transmission rate of 4%, which again can be attributed to the lower plasma viral load in HIV-2-infected pregnant women.[4]

Origin of HIV-2 and of the Epidemic

The trend of a declining epidemic raises one of the fundamental, still unanswered questions about HIV-2: which events created the epidemic, and what has changed so that the epidemic is no longer sustained? HIV-2 is genetically indistinguishable from the simian immunodeficiency virus of the sooty mangabey (SIV_{sm})[56] monkey. The natural habitat of the sooty mangabey (*Cercocebus torquatus atys*) is West Africa. Based on the large degree of genetic homology, the geographic overlap, and the fact that human–monkey contacts are common in West Africa, most researchers maintain that SIV_{sm} is the source of HIV-2.[57] In a phylogenetic tree, most subtypes of HIV-2 cluster closer to specific strains of SIV_{sm} than to each other.[58,59] Therefore it is assumed that the eight different clades of HIV-2[9–11] represent at least eight different zoonotic events.

HIV-1 is thought to originate from chimpanzee SIV (SIV_{cpz}); the exact details of this zoonotic event are unknown and are controversial.[60,61] Back-calculations using mutation rates of the viral genome as a molecular clock have estimated the timing of the original transmission from chimpanzee to human at about 1930.[62,63] In analogy to HIV-1, these back-calculations have recently been done for HIV-2. Based on partial sequences of 33 samples, the most likely date of the zoonotic event giving rise to the HIV-2 subtype A epidemic was estimated to be 1940 (± 16 years).[12]

Assuming that one person or a few persons became infected with HIV-2 clade A through contact with a sooty mangabey, it is still unclear how this led to an epidemic. It is theoretically possible that the virus used to be more virulent than it is now, but this is unlikely: there is no record of an epidemic of an AIDS-like syndrome in West Africa prior to 1985. So, if we assume that the virulence of the virus has not substantially changed over time, there must have been an increase in transmission that amplified a small outbreak into a large epidemic. This could have been due to an increase in unscreened blood transfusions on a large scale, high rates of sexual partner change, many concurrent sexual partnerships or presence of co-factors enhancing sexual transmission like sexually transmitted infections (STIs), or non-sterile injections. Several of these factors may have been present at the same time in Guinea-Bissau, especially in the period from 1963 to 1974, when a war of independence was fought against Portugal. The transmission of the virus may not be efficient enough to maintain ongoing epidemic spread in the absence of important amplifiers such as frequent commercial sex, high levels of STIs, and unscreened blood transfusions.

Marx hypothesized that re-use of unsterilized needles may have been responsible for both the HIV-1 and HIV-2 epidemics.[57] In West Africa, various mass vaccination and treatment campaigns against yaws, yellow fever, and small pox were conducted in the final decades of the colonial era,[64] and these may have been responsible for mass inoculations with HIV-2. There is no proof for this and it does not explain why HIV-2 became epidemic in Guinea-Bissau and nowhere else.

Natural History

HIV-2 infection can lead to disease manifestations, including AIDS, that are similar to those seen in HIV-1 infection. Not all infected persons progress to clinical disease, and the extent of non-progressors is not known. In Senegal 85% of HIV-2 infected women in a sero-incident cohort remained free of disease 8 years later.[65,66] In Guinea-Bissau, several persons aged over 80 years were HIV-2 infected and symptom-free; the date of infection in these octogenarians is uncertain but is presumed to be some decades ago. There are case reports of persons who have been infected 20 years or more without clinical signs and symptoms.

Although the average progression to symptomatic disease and premature death is much slower in

HIV-compared with HIV-1, fast disease progression does occur.[40] Once patients have a CD4 count below 200 cells/μL[67] or they have AIDS[67A], the mortality rate is similar to that in HIV-1. In The Gambia, the median time to death after AIDS was 12.6 months. This was significantly longer than that of HIV-1 infected patients, and the difference was attributed to the higher CD4 count at time of AIDS in HIV-2 compared with HIV-1 infected patients.[67A]

As in HIV-1 infection, lower CD4 counts are associated with symptomatic HIV-2 infection and mortality. The CD4 count is an independent predictor of mortality.[67] In a clinic-based study in The Gambia the mortality rate among HIV-2 infected women with CD4 count ≥500 cells/μL was 8.1 per 100 pyo; in those with CD4 counts between 200 and 500 cells/μL it was 18.4 per 100 pyo; and among those with CD4 count <200 cells/μL it was 83.6 per 100 pyo.[67] Also in community-based studies from The Gambia and Guinea-Bissau[5,6,13] mortality rates were significantly higher in the groups with lower CD4 counts. In the clinic-based study from The Gambia the mortality rates were similar between HIV-1 and HIV-2 infected patients with CD4 counts below 200 cells/μL, but were significantly lower for HIV-2 infected patients compared to HIV-1 infected patients in the group with CD4 cell counts ≥500 cells/μL.[67]

Plasma and Proviral Load

The plasma viral load (PVL) in HIV-2 infected persons tends to be much lower than in HIV-1 infection.[3,4,14] In a community-based sample of 130 HIV-2 infected persons in rural Guinea-Bissau, the median PVL was only 347 copies/mL.[5] In a cross-sectional clinic-based study in The Gambia, 17 of 23 asymptomatic patients (74%) had undetectable PVL.[3] In the latter study it was also shown that the PVL varied with disease stage. Among patients with CD4% >28%, the median PVL was 460 copies/mL; among those with CD4% between 14% and 28%, the median PVL was 28 000 copies/mL; and among those with CD4% <14% the median PVL was 65 000 copies/mL.[3] In a clinic-based study in Senegal, plasma viral load predicted CD4 decline in HIV-2, like in HIV-1 infection. The annual rate of decline of the CD4 count among asymptomatic HIV-2 patients was $^1/_4$ that of asymptomatic HIV-1 patients (4.1% versus 15.9%).[14] The difference in loss of CD4 cells could be attributed to the lower plasma viral load in HIV-2 infected patients, and was not determined by the HIV type *per se*.[14]

HIV-2 plasma viral load is an independent and strong predictor of mortality.[5,6,15] In a community-based study in Guinea-Bissau, the mortality rate among HIV-2 infected persons rose 1.7 times (95% Confidence Interval 1.2–2.3, $P = 0.002$) for each $\log_{10}$ increase of virus copies/mL.[5] In a study among women recruited during pregnancy in The Gambia, the mortality rate among infected persons with undetectable PVL and normal CD4% was not significantly different from that of women without HIV infection.[6] In a multivariate analysis, PVL and CD4 count were independent predictors of mortality, but HIV type (HIV-1 or HIV-2) was not.[6] Thus in HIV-2 infection, like in HIV-1 infection, plasma viral load is a crucial predictor of disease progression.

Integrated viral DNA (provirus) is the source of all plasma virions. HIV-2-infected patients have DNA viral loads similar to those in HIV-1 patients,[13,14,16,68] but the plasma concentration of virions is lower in HIV-2 infection.[3] This could be explained in several ways. Perhaps a larger proportion of HIV-1 proviruses is actively replicating. Another possibility is that in HIV-1 infection, more DNA is integrated and replication-competent compared with HIV-2. It is also possible that in HIV-1 infection, high proviral DNA levels exist in other compartments than blood. Finally, it may be that HIV-2 virions are cleared more efficiently.[14] In six long-term non-progressing HIV-2 infected patients with undetectable plasma viral load and normal CD4 counts, it could be demonstrated that replication-competent virus was present in peripheral blood mononuclear cells (PBMCs), albeit at extremely low concentrations.[69]

Clinical Features

Although clinical AIDS in HIV-2 is similar to that in HIV-1, a few differences have been observed. Despite a similar prevalence of HHV8 infection, HIV-2 infected subjects had a much lower incidence of Kaposi's sarcoma in a study from The Gambia.[17] An autopsy study from Cote d'Ivoire found that HIV-2 infected patients were more likely to have severe multi-organ cytomegalovirus (CMV) infection, HIV encephalitis, and cholangitis than HIV-1 infected patients, suggesting a more prolonged terminal disease course.[70] Tuberculosis (TB) is a major opportunistic infection for HIV-2 infected patients, and its incidence increases strongly with decreasing CD4 counts.[71] In a clinic-based study from The Gambia, no difference in TB incidence was observed between HIV-1- and HIV-2-infected persons with similar CD4

counts. A study among hospital patients in Dakar found that chronic diarrhea and diarrhea caused by bacterial infections were more frequent in HIV-2 compared with HIV-1-infected patients with AIDS; oral candidiasis and chronic fever were more frequent in HIV-1 patients with AIDS.[72]

The median CD4 count among HIV-2 patients with AIDS varied between 73 and 358 cells/μL in several studies from West Africa and Paris.[39, 67A,72–75] In a clinic-based study in The Gambia, the median CD4 count at the time of AIDS diagnosis was 176 cells/μL in HIV-2 patients ($n = 87$), which was significantly higher than the 109 cells/μL in HIV-1 patients ($n = 341$).[67A]

The median CD4 count near the time of death was found to be between 61 and 146 cells/μL in HIV-2 infected patients.[67A,70,76] This is higher than the usual CD4 count at time of death reported from HIV-1 infection, but most studies on HIV-1 were done in developed countries with better end-of-life care than in most of Africa.

One of the first epidemiological studies on HIV-2, conducted in Bissau in 1987–1988,[77] showed that the mortality associated with HIV-2 infection was much lower than that usually found in HIV-1 infection. All subsequent studies have confirmed this.[5,6,53,67,73,78] In a seroprevalent clinical cohort in The Gambia, HIV-2 patients had a lower mortality than HIV-1 patients, but this lower mortality was limited to those with a normal CD4 count (>500/μL). Among those with a CD4 count <200/μL, the mortality rate was similar between HIV-1- and HIV-2-infected subjects.[67] This could be explained in two ways. The first possibility is that all HIV-2-infected subjects experience a deterioration of their immune system, but this decline is slower than in HIV-1 infection. Once the CD4 count has declined to below 200/μL, patients are at high risk of fatal opportunistic infections and there is no difference in mortality. The other possibility is that those with HIV-2 infection fall in either of two categories: those whose immune system is not affected at all by the infection, and those whose immune system is damaged by the infection, at a rate similar to HIV-1. This question is unresolved and long-term follow-up of an incident cohort would be required to answer it.

HIV-2 infection in children is rare, even in endemic areas, due to the low mother-to-child transmission risk of 4%.[4] There are few data on the clinical course of HIV-2 in children. In the only prospective long-term observational study of children with perinatally acquired HIV infection (median follow-up time 6.6 years), conducted in The Gambia, three out of eight HIV-2 infected children died (38%) compared with 12 out of 17 HIV-1 infected children (71%) and 40 out of 448 children of HIV-uninfected mothers (9%). The mortality rate of HIV-2-infected children was significantly higher than that of uninfected children ($P = 0.02$), but the difference with HIV-1-infected children did not reach statistical significance ($P = 0.08$).[79]

HIV-1 and HIV-2 Interactions

Dual Infection

Using type-specific antibody tests, it became evident that both HIV-1 and HIV-2 circulated in West Africa. Samples of some people in West Africa showed dual serological reactivity, and it was not clear whether this was mainly due to antibody cross-reactivity, dual infection, or an infection with a third, unknown virus.[80] Quite early on, it was demonstrated by PCR that dual infection with both HIV-1 and HIV-2 did occur.[81,82] Later improvements in PCR techniques showed that a large proportion of people with dually reactive samples (up to 86%) is truly dually infected.[83,84]

HIV-2 does not Protect against HIV-1 Infection

In 1995, Travers and co-workers[85] reported that HIV-2 seemed to offer protection against subsequent HIV-1 infection in a cohort of commercial sex workers in Dakar; this caused excitement and hope as it could lead to the development of a vaccine against HIV-1.[18] Several research groups in Guinea-Bissau,[34,86] Cote d'Ivoire,[87,88] and The Gambia[89,90] examined this putative effect in other cohorts. None of the seven analyses so far have been able to reproduce this finding, so currently available epidemiological data do not support a protective effect of HIV-2 infection against incident HIV-1 infection.[91] The investigators of the cohort in which the original finding was made, have provided no updates of the effect in that cohort since 1999,[66,92,93] so it is unknown whether the effect in that cohort persisted, or declined over time, or even reversed. Two studies compared the distribution of HIV-1 subtypes among singly infected and HIV-1 and HIV-2 dually infected subjects, and found no differences in frequencies.[94,95] This argues against a possible protective effect of HIV-2 that is limited to certain HIV-1 subtypes.

HIV-2 does not Protect against Progression of HIV-1 Disease

Two cross-sectional studies from West Africa have examined the pattern of PVL and CD4 count in dually infected patients. In these studies it was found that in patients with low CD4 counts, the PVL of HIV-1 is very high and that of HIV-2 very low.[96,97] This contrasts with singly infected HIV-2 patients with low CD4 counts, in whom the PVL tends to be high.[3,96] In dually infected patients with normal CD4 counts, the PVL of HIV-2 tended to be comparable with that in singly HIV-2 infected subjects. In all CD4 strata, the PVL of HIV-1 appeared similar to that in HIV-1-singly infected subjects.[96] This suggests that in patients with progressing immunodeficiency, HIV-1 is out-competing HIV-2, and that the disease progression is dictated by HIV-1 rather than HIV-2.

There is only one long-term study analyzing the survival and mortality of subjects with dual HIV infection.[67] Among patients of the genito-urinary (GU) clinic in Fajara, The Gambia, the mortality rate of 107 dually infected patients was similar to that of HIV-1-infected patients, and worse than that of HIV-2-infected patients. This was true overall, and after adjusting for baseline CD4 count. These data do not support suggestions that HIV-2 infection could mitigate the course of HIV-1 infection.

HIV-1/HIV-2 Recombination

If a person is infected with two or more subtypes of HIV-1, these can re-combine their genomes to form new strains of HIV-1, and these can be transmitted. Some of the recombinant strains are successful in spreading, e.g. CRF01_AE in Thailand and CRF02_AG in West Africa.[98] Recombinations of the genetically rather distant groups O and M have been described,[99–101] but so far no recombinations of HIV-1 and HIV-2 have been reported. Construction of chimeric HIV-1/SIV viruses indicate that this is biologically possible.[102,103] Curlin and co-workers[104] searched for recombinations in the *env* gene of 46 dually infected patients in Senegal, but found none. It is possible that these recombinations are very rare or that their productive existence is constrained by biological factors.[104]

Treatment of HIV-2 Infection

As PVL and CD4 count are key predictors of disease progression in both HIV-1 and HIV-2,[5,6,14,15] it appears logical to use the same principles in their treatment. The mortality rate of HIV-2 infected subjects with undetectable PVL and normal CD4 count is not increased compared with uninfected people,[6] and these people may never need treatment. Randomized controlled clinical trials for treatment of HIV-2 infection have not been done, and at the time of writing, there are no agreed international treatment guidelines specific to HIV-2. Available clinical data are case reports,[105,106] case series,[41,39,107] and cohorts.[108,109] The suggestions for treatment given here are based on the few available clinical data, on *in vitro* studies, and on extrapolation of what is known from treatment of HIV-1 infection.

Initiating Treatment

ART should be started when the patient has AIDS. Symptomatic, non-AIDS, disease should not be an indication for treatment, as the symptoms or conditions may be unrelated to HIV-2. This is especially important in sub-Saharan Africa, where the background incidence of HIV-associated conditions is relatively high.[110] Patients with a CD4 count <200 cells/μL should be started on ART. For those with a CD4 count between 200 and 350 cells/μL, ART should be considered, and those with CD4 counts above 350 cells/μL should be monitored but treatment could be deferred (Table 56.2).

Objective of Treatment

The objective of treatment should be to reduce the PVL to undetectable levels. As there is no commercially available plasma viral load assay, it will be difficult in practice to monitor PVL outside specialized research centers where in-house assays have been developed.[3,14,19,111–113] Therefore monitoring of

Table 56.2 Suggested guidelines for initiating antiviral therapy of patients with HIV-2 infection

Disease stage		Recommendation
Clinical	CD4 count	
AIDS	Any CD4 count	Start ART
Symptomatic or asymptomatic	≤200 CD4 cells/μL	Start ART
	>200 and ≤350 CD4 cells/μL	Consider ART[a]
	>350 CD4 cells/μL	Defer ART

[a]When plasma viral load is high (e.g. >10 000 copies/mL), there is more reason to start ART than when plasma viral load is low.
ART, antiviral therapy.

CD4 count may be the only option, but this will be showing treatment failure at a later stage than monitoring plasma viral load.

Resistance and Adherence

HIV-2 is inherently resistant to the non-nucleoside analog reverse transcriptase inhibitor (NNRTI) class of drugs.[20,114–116] The virus can become resistant to nucleoside-analog reverse transcriptase inhibitors (NRTIs) and to protease inhibitors (PIs).[41,117] Although no data are available, it is assumed that adherence is as crucial in HIV-2 as in HIV-1 to prevent resistance formation and maintain suppression of plasma viral load. In recent years, resistance mutations in HIV-2 have been identified, but the interpretation of genotypic resistance data in HIV-2 is difficult and no agreed guidelines exist.[118–120] Some mutations appear to have the same significance as in HIV-1 infection (e.g. M184V conferring resistance against lamivudine and Q151M conferring resistance against NRTIs),[108,109,121] but other mutations may have an impact different to that in HIV-1.[118,119]

Choice of Drugs

Although *overall,* HIV-2 is a less virulent virus than HIV-1, patients that have progressing infection, with HIV-associated symptoms, high PVL, and decreasing CD4 count, have a poor prognosis, similar to HIV-1 infected patients.[6,67] Therefore they should be treated as vigorously as HIV-1-infected patients, with at least three drugs. NNRTIs are not active against HIV-2.[20,114–116] NRTIs and PIs are effective, although clinical studies suggested that nelfinavir is less effective against HIV-2 than against HIV-1.[41,108,109] Amprenavir and atazanavir are not active against HIV-2 *in vitro*.[20,116] In *in vitro* studies, HIV-2 strains appeared to be naturally resistant against the fusion inhibitor enfuvirtide.[116] This means that there are far fewer therapeutic options for HIV-2 patients. A first option could be a combination of two NRTIs and a boosted PI, e.g. indinavir or lopinavir.[109] The choice of a salvage regimen will be even more restricted than in HIV-1.[109,119]

Long-term Benefits

There are no data showing the long-term benefits of ART in HIV-2. A study of 18 ARV treated patients in Cote d'Ivoire showed a doubling of the CD4 count after 12 months of treatment, from 82 to 163 cells/μL, but this was not statistically significant.[108] In The Netherlands, 11 out of 13 HIV-2-infected patients treated with ZDV-3TC-IND/RTV had successful suppression of plasma viral load during the entire course of treatment (median duration 91 weeks, range 52–234 weeks). The CD4 count increased from a median 90 cells/μL to a median 270 cells/μL.[109]

Treatment of HIV-1 and HIV-2 Dual Infection

Some patients are infected with both HIV-1 and HIV-2 and in West Africa this is not uncommon.[67] In these patients HIV-1 is the virus that dictates disease progression, with low HIV-2 PVL and high HIV-1 PVL.[96,97] This has led some researchers to advocate that treatment should be directed against HIV-1 only.[97] This may be dangerous as exemplified by a patient whose HIV-1 PVL was successfully suppressed, but who nevertheless progressed due to unsuppressed HIV-2 PVL.[122] Therefore, drugs should be chosen that cover both infections, so NNRTIs, some PIs (e.g. nelfinavir and amprenavir), and enfuvirtide should be avoided.[20,116]

Treatment of HIV-2-Infected Children

Mortality among children with HIV-2 is higher than in seronegative children and this suggests that children with HIV-2 infection need the same care as HIV-1-infected children. There are no published data from clinical trials or even cohort studies or patient series that could guide the treatment of HIV-2-infected children. The same principles as in treatment of HIV-1-infected children should guide the management of pediatric HIV-2 infection, with the caveat about the choice of antiretroviral drugs mentioned above.

Conclusion

HIV-2 is an infection of public health interest in West Africa, where up to 2 million people may be infected; an unknown proportion of these will suffer from HIV-2 induced immunodeficiency and premature mortality. Antiretroviral treatment is effective against HIV-2, but no evidence-based guidelines for treatment exist. It is suggested that principles and guidelines for treatment of HIV-1 are used, while avoiding the use of NNRTIs, which are not effective against HIV-2, some protease inhibitors (amprenavir, nelfinavir), and enfuvirtide. HIV-2 is a human model for HIV-1 infection and elucidation of its lower pathogenicity may provide clues for an effective vaccine against HIV-1.[21]

There are four crucial questions regarding HIV-2 that are unanswered. The first question is: Why did a zoonotic event lead to a localized HIV-2 epidemic in Guinea-Bissau and why is this epidemic now in decline? In recent decades, several animal pathogens jumped the species barrier and caused epidemics in humans (among others: HIV-1, HIV-2, the corona virus causing SARS, Ebola virus, prions causing variant Creutzfeldt–Jakob disease). In the case of HIV-1 and HIV-2, some widely discussed hypotheses have held medical interventions responsible for the epidemics. It seems important to trace the origin of these epidemics, whether that means confirming or rejecting these hypotheses. Phylogenetic analyses on a larger scale than have been done so far, and epidemic modeling studies that try to fit the existing data, can contribute to answering this question.

The second question is: What proportion of people that are HIV-2-infected develop immunodeficiency or AIDS, and die prematurely? This proportion needs to be known to better understand the pathogenesis of HIV-2 infection, to inform patients about their prognosis, and to help identify factors that may determine non-progression. Estimates based on prevalent cohorts are biased; long-term follow-up of seroconverters is needed to answer this question. There are few such cohorts and all are small; collaboration between research groups in West Africa could help to answer this question.

The third question is: Why does HIV-2 infection usually not lead to high plasma viral loads, in spite of proviral loads similar to HIV-1? This could be due to characteristics inherent to the virus, or to a more efficient immune response, or to generally lower levels of immune activation. This question could be examined by detailed comparative virological and immunological studies.

The final unanswered question: Is the virological, immunological, and clinical response of HIV-2 infected people to highly active antiretroviral therapy similar to that in HIV-1-infected people? The first observational data are suggesting this is the case. In order to establish effective, evidence-based treatment regimens for HIV-2 disease, clinical trials and cohort studies of antiretroviral therapy should be conducted in HIV-2-infected patients.

Acknowledgments

I would like to thank Hilton Whittle, Koya Ariyoshi and Andreas Hansmann for their comments on a draft of this chapter.

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