# HIV INFECTION
## AGEING, INFLAMMATION AND COMORBIDITIES

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# HIV Infection, Ageing, Inflammation and Comorbidities

*From the end of the 2000s, after the introduction of the first antiretroviral therapies (ART), it became clear that the benefits of these treatments were considerably greater than their side effects, especially when introduced early. The recommendation at present is to begin treatment with ART as soon as CD4 T-cell count falls below the normal level of 500/mm$^3$.*

*However, in spite of major progress made in treating HIV, these drugs cannot eradicate the infection and must be taken for life. In addition, while ARTs are very effective at preventing AIDS, a lethal complication of the infection, another complication of HIV infection has been discovered. Long considered, incorrectly, as a side effect of treatment, this infection, once it has become chronic and a source of comorbidities, causes long-term systemic inflammation. This infection of the immune system induces a chronic, general inflammation that leads to accelerated ageing of the immune system. It also leads to cardiovascular, bone and neurological complications, as well as contributing to the emergence of cancers, independently of the immune deficiency. The complications of chronic inflammation are all the more serious the later the treatments are initiated.*

*However, fresh hopes are emerging with the most recent epidemiological data suggesting that early introduction of ARTs, and continuing them without interruption, could eventually limit the incidence and severity of comorbidities associated with the chronic inflammation caused by HIV.*

## THE VICIOUS CIRCLE OF IMMUNE ACTIVATION AND INFLAMMATION INDUCED BY HIV INFECTION

The mechanisms behind this inflammation are not currently fully understood; they appear to be multifactorial. Within a week of the HIV invasion (Stacey et al), the innate immune responses trigger, as for any other virus, a formidable activation of white cells, in particular those targeted by the virus: the CD4+T cells and macrophages. It also induces the overproduction of a large number of soluble factors, alpha interferon and cytokines and chemokines known as pro-inflammatory, creating a systemic and permanent activation.

In addition, the viral invasion leads to the activation of immune defences specific to the virus, mediated by the auxiliary CD4+ T cells, killer or cytotoxic CD8 cells and antibody producing B cells. These defences enable the level of viral replication be partially controlled, but does not eliminate the virus. It leads to a generally low-level viral replication that maintains the chronic inflammation caused by the innate immune system and the chronic activation of the specific immune defences, which also maintain the inflammatory state due to the secretion of cytokines.

If untreated, these phenomena lead to the exhaustion of the immune system, aggravating the deficiency caused by the infection, and induce progressive tissue damage in lymphoid tissues where the virus is replicated, mainly in the mucosa-associated lymphoid tissue (MALT) (Appay et al). The objective change produced by increasing deposits of collagen is associated with abnormalities of the intestinal barrier, which cause an increase in microbial translocation phenomena or an abnormal transfer of commensal bacteria from the intestinal lumen into the mucosa wall. The local destruction of these bacteria is thought to release highly pro-inflammatory degradation products such as lipopolysaccharide (LPS) or flagellin, both locally and in the systemic circulation (Brenchley et al).

These microbial products, by binding to so-called «danger» receptors on the surface of the macrophages activate production by these immune cells of various pro-inflammatory mediators such as tumour necrosis factor (TNF), interleukin-6 (IL-6), IL-1b, macrophage-inflammatory-protein (MIP)-1a, MIP-1b and RANTES, but without a high elevation of the most standard marker for inflammation, CRP. Tests for plasma levels of these products give results that are controversial due to their high instability, and difficulty in standardisation, which limits their use in clinical practice, even if there is an international consensus recognising the causal link between HIV infection, a moderate increase in serum levels of these molecules and low-grade chronic inflammation. There are also associated abnormalities in the activation and number of innate immune cells (monocytes and polynuclear leukocytes).

This chronic inflammatory environment aggravates the destruction of the CD4+ T cells and the immunodeficiency related to chronic viral infections frequently associated with HIV infection, causing the loss of control and reactivation of hepatitis B (HBV) or C virus (HCV), cytomegalovirus (CMV) or Epstein-Barr virus (EBV). These viral infections themselves activate both the immune defences and the immune responses specific to these agents, further amplifying the chronic immune activation caused by the HIV itself, creating, if untreated, a vicious circle of inflammation / immune exhaustion / virus reactivation. In addition to the serum markers, cell activation markers, such as the abnormally elevated expression of HLA-DR or CD38, persist on the surface of the CD4 and CD8 T cells, tests which are also difficult to standardise and therefore not used in clinical practice.

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## PERSISTENCE OF INFLAMMATION AND IMMUNE ACTIVATION UNDER EFFECTIVE ANTIRETROVIRAL TREATMENT

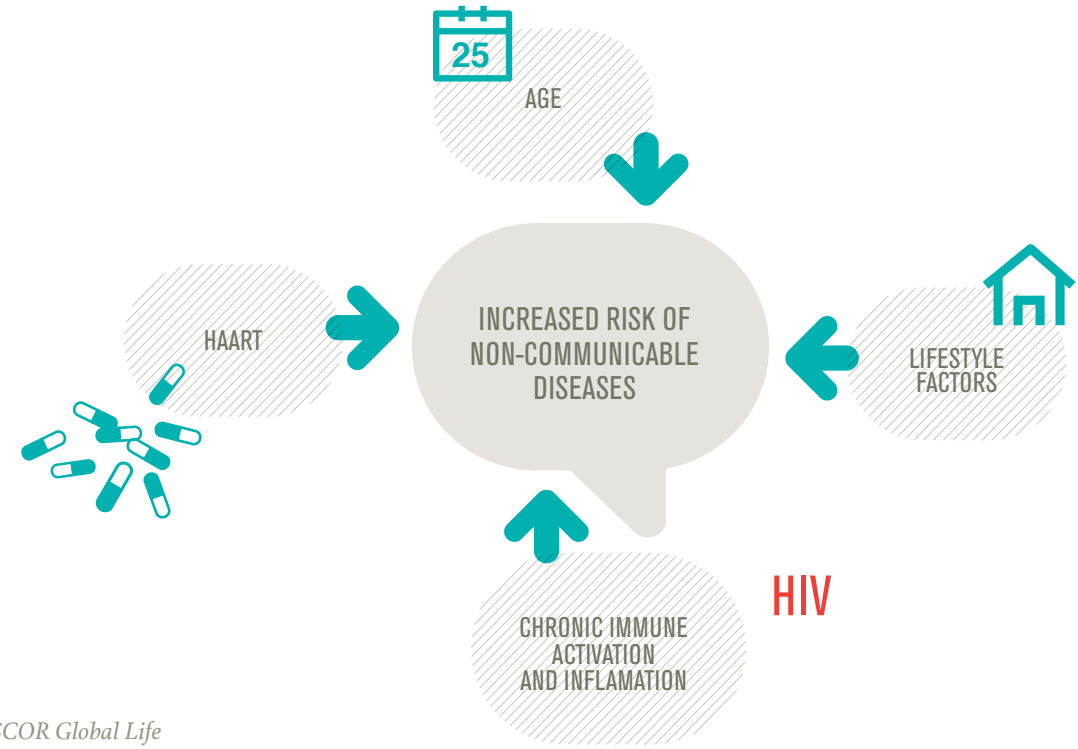
One of the most spectacular benefits of ART, regardless of the stage at which it is introduced, is the regression of these different anomalies and markers of activation and inflammation (Autran et al). However, it is rare that ARTs lead to complete normalisation of these values and it is still very common to see abnormal activation/inflammation levels persisting in treated patients with no detectable viral replication over the long term (Hunt et al, Funderburg NT et al, Krishnan S et al). Nonetheless, even if the level of residual viral replication is correlated with cell activation, it is not a good predictor of it (Hatano et al).

The most recent research has shown that low-level viral replication persisted in the tissues of treated patients with an undetectable viral load and was associated with persistence of this immune activation, certain therapy intensifications have led to a reduction in immune hyperactivation (Buzon et al).

The scale of these residual anomalies is very closely linked, even after many years of treatment, to the nadir CD4 count (the lowest CD4 count measured before treatment). The «Nadir effect» reflects the severity of immunological damage induced by the virus and by the years of untreated exposure to the virus.

The persistence of viral coinfections plays an important role in the persistence of these anomalies. Thus the introduction of a 6 month-long anti-cytomegalovirus (CMV) therapy was found to reduce the T cell activation levels (P Hunt et al). Nevertheless, the current toxicity of anti-CMV drugs has not allowed this interesting observation to be extended any further.

**HIV INFECTION AND THE RISK OF COMORBIDITIES**




*Source : SCOR Global Life*

## COMORBIDITIES RELATED TO HIV INFECTION, BUT NOT AIDS

Today a series of comorbidities, known as «Serious non-AIDS events» or SNAEs, is associated with HIV infection, even when treated and independent of AIDS. The first comorbidity discovered was increased cardiovascular risk, which can reach a factor of 2 to 3, but was initially thought to be a complication of the treatments. Recent data appears to be less alarmist with a relative risk of myocardial infarction of 1.6 compared to the general population (Islam et al).

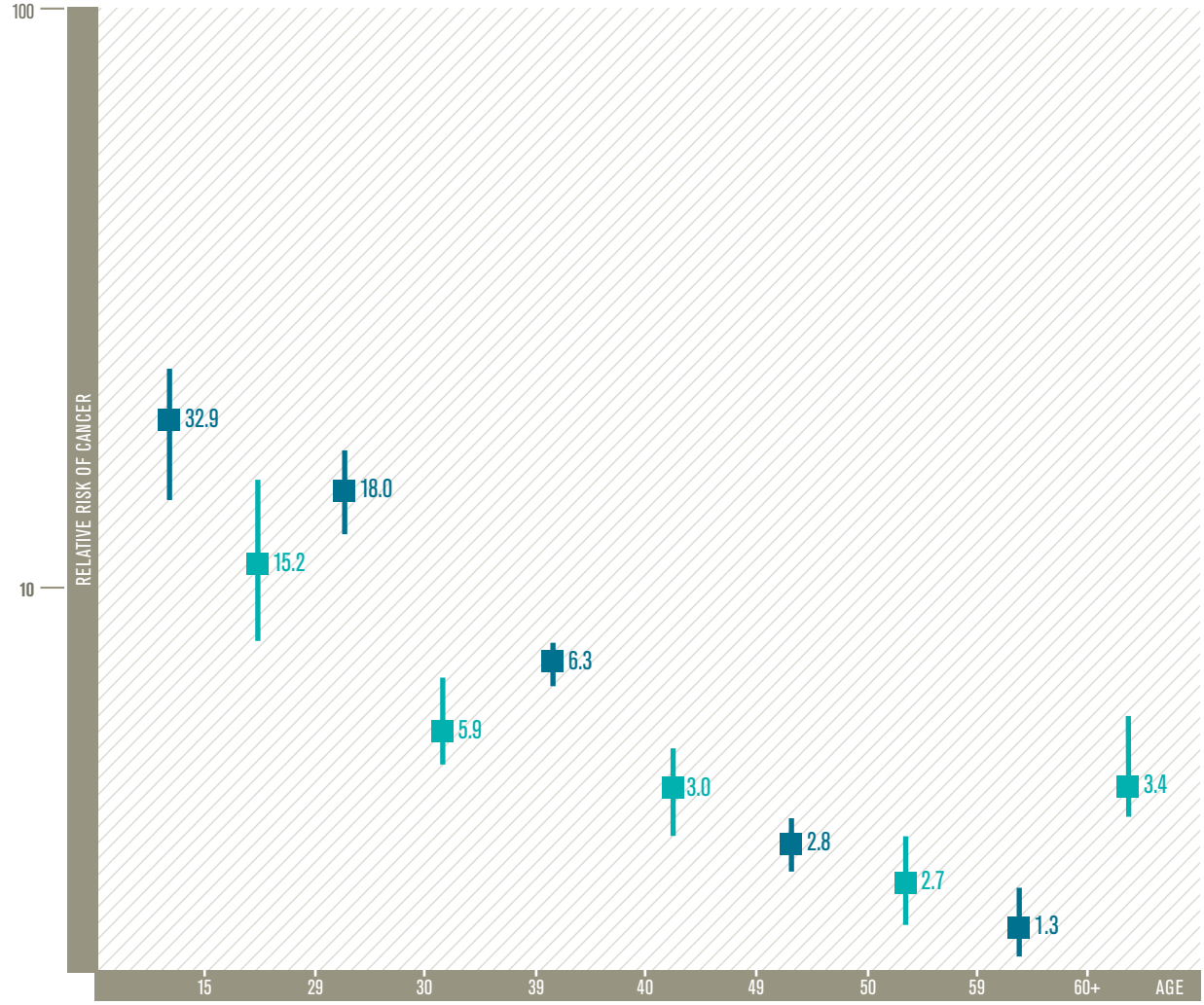
The accountability of HIV in regards to cardiovascular risk was revealed by the «SMART» trial (N ENGL J Med) and is evidentially associated with classic risk factors for MI. Recently, a level of residual viral replication above a threshold of 50 copies/mL, but not the nadir CD4 count, was reported as an increased risk factor for MI (RR 1.5). The years of exposure to ARV drugs containing 1st generation protease inhibitors also seems to be a risk factor, which could disappear with new generations of ARVs, although not enough time has passed yet to be sure (d'Arminio Monforte et al). Metabolic disorders such as insulin resistance, hypercholesterolemia, reduced HDL cholesterol, abnormal coagulation activation and, above all, tobacco consumption are obviously associated with this excess cardiovascular risk (Lang et al). The persistence of CMV coinfection and the activation of the anti-CMV immune defences have also been associated with arterial wall damage.

Other conditions, such as the risk of spontaneous fractures linked to osteoporosis, are connected to the chronic inflammation and metabolic disorders induced by HIV infection, with an excess risk of about 1.5.

Along with myocardial infarction, the increase by a factor of 2 to 3 in the frequency of cancers unrelated to AIDS remains the main comorbidity. This increase in cancers is observed at equal ages compared to the general population and concerns not only virus-induced cancers (linked to EBV, HBV, HCV or HPV), but also cancers not induced by oncoviruses. The ONCO-VIH national prospective study conducted by the teams at UPMC and La Pitié-Salpêtrière with the ANRS (national French AIDS research agency) showed a cancer incidence rate of 14 per 1,000 person-years with a relative risk around 3.5 compared to the general population. The cancers most frequently involved, besides non-Hodgkin's lymphoma (21.5%) and Kaposi's sarcoma (16%) were lung cancer (9.4%), anal cancer (8.2%), Hodgkin's lymphoma (7.6%), skin cancers (6.8%) and liver cancer (5.6%) (Lanoy E et al).

> "The increase by a factor of 2 to 3 in the frequency of cancers unrelated to AIDS remains the main comorbidity"

## RELATIVE RISK OF CANCER IN HIV-INFECTED PATIENTS BY GENDER AND AGE




| | MEN | WOMEN | MEN | WOMEN | MEN | WOMEN | MEN | WOMEN | MEN | WOMEN |
|---|---|---|---|---|---|---|---|---|---|---|
| OBSERVED | 27 | 19 | 188 | 82 | 378 | 113 | 268 | 61 | 155 | 59 |
| EXPECTED | 0,8 | 1,3 | 10,4 | 13,9 | 60,1 | 37,5 | 94,6 | 22,3 | 121,9 | 17,5 |

*Relative risk of cancers in HIV infected patients by gender and by age as compared with the general population in France. The relative risks shown as squares, with surrounding 95% confidence intervals as vertical lines.*
*The number of observed cancers is specified, as well as the number of expected cancers based on the age-and-sex specific incidence in the general population.*
*Source : Lanoy et al. The ONCOVIH study. Int. J. Cancer: 129, 467-475 (2011)*

## PATHOGENESIS OF HIV INFECTION COMORBIDITIES:

**Inflammation ?**
**Immune deficiency?**
**Or accelerated ageing?**

One of the easiest factors to connect the appearance of HIV infection-related comorbidities is the advancing age of patients, with over 25% of people (male and female) living with HIV in 2012 aged over 45 according to European cohort data (Eurocoord). The pathogenesis of these complications involves the sequence described above from HIV infection to activation of macrophages and their release of pro-inflammatory cytokines which leads to fibrosis of the lymphoid tissues, the aggravation of atheromatosis plaques, the deregulation of the hemostasis system, metabolic syndrome and immunosenescence. It remains very difficult to predict the occurrence of these comorbidities using serum or cell activation markers. A controlled prospective study recently compared these markers before and one year after the initiation of ART with successful viral replication control in patients developing SNAEs (myocardial infarction, non-AIDS-related cancers, bacterial infections or death). The subjects were matched for age, gender, CD4 count, pre-therapy viral load and ART combinations. The results confirmed the links between occurrence of these conditions and the abnormal inflammation serum markers. The results did not confirm a link with cell activation markers (Tenorio et al), the most strongly associated marker being IL-6 and D-Dimers, conferring a relative risk of infarction of 2 or 3. Hence, the inflammatory markers associated with these comorbidities are the same as the inflammatory markers classically associated with atherosclerosis.

The role of chronic inflammation in the excess cancer risk is not definitely established, whereas as the role of immune deficiency does seem to be confirmed. Thus, the excess risk of lung cancer appears to be 3.4 at a CD4 count of between 200 and 350, but it falls to 1.2 between 350 and 500, and then disappears at counts above 500 CD4/mm$^3$.

This pattern has not been confirmed for other cancers, such as Hodgkin's lymphoma, whose excess risk remains at 13.5, nor for the excess risk of anal cancer which was found to be 33.8 (at CD4 counts equal to or above 500/mm$^3$) in large cohort studies in the USA (Kaiser Permanente) and France (FHDH) (Silverberg et al). However, the number of years spent under the 200 CD4/mm$^3$ threshold confers a greater risk than does the current count for these lymphocytes.

So, the accelerated ageing of the body has frequently been implicated in these different comorbidities, but is this really the case? According to the French FHDH cohort study, MI occurs at the same age in PLWH as in the general population (Lang et al). On the other hand, the increased risk of the cancers mentioned above seems to occur in HIV-positive subjects at a younger age than in the general population, although the fact that 70% of PLWH are between 30 and 50 must be taken into consideration.

# CONCLUSION

*How will these comorbidities progress?*

*The links between inflammation or low CD4 count and related comorbidities being clearly proven, it is important that patients do not have CD4 counts below 500/mn$^3$.*

*The aims of the new therapeutic indications are not only to reduce the transmission of infection but also the frequency of comorbidities. Early treatment and new generations of ART both play a beneficial role in limiting these comorbidities.*

*It is hoped that the excess risk will disappear in years to come although it is too early to draw any definite conclusions. In fact, the benefit is unfortunately limited to HIV infections that are diagnosed and treated. However, it is reasonable to expect that better education of the medical community and of HIV-infected people on the multiple benefits of these new therapeutic recommendations will enable earlier diagnosis and treatment of this serious disease.*

## INSURANCE INSERT

**Insurers have remained prudent until now on the subject of ageing and HIV infection due to the lack of epidemiological data on the population concerned.**

From the studies published in recent years, it is clear that the profile of people infected with HIV is changing. Since the introduction of triple therapy and the resulting reduction in mortality, infected people are living longer and their average age is rising accordingly. In the ATHENA cohort (Holland) the average age in 2010 was about 44 and it is estimated for the year 2030 at about 57[1, 2]. Under these conditions, we can expect to see the occurrence of age-related comorbidities, such as myocardial infarction and certain cancers, which are 2 to 3 more common in this population. At the same time, though, the data published on cognitive disorders in HIV positive people[2] in the ageing population have led insurers to remain very prudent.


[1] *Smit M, Brinkman K, Geerlings S and alls. Future challenges for clinical care of an ageing population infected with HIV: a modelling study. Lancet Infect Dis 2015; 15: 810–18*

[2] *Vance DE. Cody SL. Predictions of geriatric HIV in 2030. Lancet Infect Dis 2015; 15: 753-75*

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