



Recent advances in the treatment of HIV infection

An HIV epidemiological shift & changing paradigms in HIV care

A review of the long-term insurability of HIV infection in resource-rich countries

Following the emergence of HIV (human immunodeficiency virus) in the 1980s, research demonstrated an infection characterised by an intense viraemia with ongoing replication and early dissemination to multiple tissues of the human body.

Rapid destruction of immune cells occurred within weeks of initial infection.¹ Furthermore, the virus was shown to be one that constantly mutated – a process which started early on in the infection.

Ultimately HIV infection resulted in a disease against which the host's immune reaction could not protect itself and, with limited treatment options on offer at the time, significantly impacted the mortality of infected individuals.

All of these factors combined to present the long-term life industry with an uninsurable medical risk which for the most part was and still is managed upfront at the policy underwriting stage through an HIV screening test.

With recent advances in the treatment of HIV infection combined with an improved understanding of the nature of the infection, a paradigm shift has occurred in the approach to caring for HIV-infected individuals. The result has been significant changes in the epidemiology of HIV as well as associated HIV mortality. Consequently, it may be necessary for life industry markets to review their current practices when it comes to HIV-positive individuals and long-term insurance.

Treatment models

With the introduction of antiretroviral drug monotherapy (AZT) in 1987 followed by dual-drug therapy in 1991 and three-drug combinations (aka HAART or Highly Active Antiretroviral Therapy) in 1996, the initial HIV treatment approach was one of early intervention – e.g. the so-called “hit hard and hit early” approach with treatment initiated once CD4 T cell counts dropped below 500 cells/ μ L.²

¹ Brenchley JM et al. Pages 749-759
Miller S. Slides 2-8; 12-14

² Bartlett JG.

Palliative versus individualised care

A number of factors, such as drug toxicities, emerging drug resistance, complicated drug dosing regimens and medication expenditure, did, however, result in a move away from this early intervention model towards a “palliative care model” of delayed intervention whereby treatment was withheld in patients with relatively preserved CD4 T cell counts (treatment only initiated once CD4 < 200 cells/μL and later once CD4 < 350 cells/μL). These palliative models focused on programmatic treatment rather than individualised care and extended life expectancy on average by 8 – 10 years. Adverse outcomes observed from this model included:

- Inadequate immune restoration resulting in new and unexpected illnesses
- Treatment failure with the emergence of drug-resistant HIV strains³

With the arrival of newer treatment regimens offering greater short- and long-term safety, increased antiviral efficacy, high tolerability and fewer drug interactions, the pendulum has swung back to early intervention in order to specifically address the palliative model’s adverse outcomes.

There is now evidence to show that early intervention limits and prevents viral mutation, prevents immune cell depletion and furthermore reduces transmission.⁴

The result has been significant improvements in life expectancy, giving credence to the idea of HIV as yet another chronic insurable illness.

It may be necessary for life industry markets to review their current practices when it comes to HIV-positive individuals and long-term insurance.

³ Miller S. Slides 2-8; 12-14
Bartlett JG.

⁴ Miller S. Slides 2-8; 12-14

Emphasis on early virological suppression

Based on data accumulated over two decades it has been shown that cytotoxic T lymphocytes (CTLs) are key to the control of HIV infection. Studies have shown that if anti-retroviral treatment is not started during the early phase of HIV infection, the capacity of CTLs to secrete necessary anti-viral cytokines and chemokines and generate cytotoxic granules in response to continuous HIV antigenic stimulation starts to diminish.⁵

Furthermore, it has been shown that if untreated there is an early accumulation of mutations of the virus in T cell epitopes (the viral antigen presented to the immune system) that allows the virus to escape recognition by the circulating CTLs, also giving rise to repeated viral antigenic stimulation and ultimately promoting T cell dysfunction.⁶

The preservation of polyfunctional HIV-specific CTLs is therefore paramount for the long-term fight against HIV infection in order to improve mortality outcomes in HIV-infected individuals (see Table 1). Evidence shows that this is best achieved through early intervention.⁷

Table 1: Mortality outcomes in HIV +ve individuals on antiretroviral therapy (ART)⁸ 35-year-old male

CD4 T cell count (cells/μL)	Degree of viral suppression	Attained Age (years)	Estimated Excess Mortality Rate (%) †
< 200	Fully suppressed	71	+450
200 - 350	Fully suppressed	77 – 80	+150
200 - 350	Incompletely suppressed	54	+1,000

† based on US pricing models

⁵ Rowland-Jones S et al. Page 0721
Altfeld M et al. Page 177

⁶ Rowland-Jones S et al. Page 0721
Altfeld M et al. Page 177

⁷ Miller S. Slides 2-8; 12-14
Rowland-Jones S et al. Page 0721
Altfeld M et al. Page 177

⁸ Miller S. Slides 2-8; 12-14

Computer-simulated results reported in a European study looking at long-term insurability of HIV-infected individuals showed similar mortality outcomes (as shown in Table 1) for a newly diagnosed 30-year-old UK male with a favourable HIV risk profile i.e. no comorbid Hepatitis C infection and a high CD4 at the start of ART. According to the study, the predicted age of death was 75 with a 95% confidence interval of 68 – 77 years.⁹

Epidemiological shift

Between 2004 and 2007 the number of adults aged 50+ living with HIV has grown by 14% a year. Data also shows that in developed countries the population with HIV is growing and aging, with 50% of those with HIV in the USA expected to be aged 50 or older in 2015.

The two phenomena driving the aging of the HIV epidemic in resource-rich settings (defined as countries with easy access to potent ART) are:

1. The functional immunological improvement resulting from the efficacious virological suppression from current ART
2. Middle-aged and older individuals becoming infected¹⁰

Changing spectrum of disease

The outcome of the new HIV care paradigm and epidemiological shift is a change in the spectrum of HIV-related diseases. AIDS-defining diseases are becoming increasingly rare and variably associated with outcome, i.e. no longer inevitably fatal. Instead, we are experiencing a widening spectrum of putative non-HIV-related diseases, which are increasingly predicted to become the leading causes of death, particularly in middle-aged and older populations¹¹ (see Table 2).

Table 2: Proportion of deaths due to non-HIV related events in HIV +ve individuals¹²

Age	CD4 T cell count (cells/ μ l)	Viral load (copies/ml)	Proportion of deaths due to non-HIV-related events
35-year-old:	200	1,000,000	6%
	800	10,000	45%
50-year-old:	200	1,000,000	20%
	800	10,000	80%

A growing body of work that has analysed incident disease and controlled for important risk factors in HIV-positive individuals demonstrates an increased risk of non-HIV-related conditions which include non-HIV-related cancers (anal, oral, head and neck, liver, lung and testicular carcinomas), pulmonary disease, intracranial haemorrhage, cardiovascular disease and osteoporosis.¹³ Additionally, it is non-HIV-related cardiovascular and liver diseases and cancers that are the main causes of non-HIV-related mortality in HIV-infected individuals (see Table 3).

Table 3: Causes of non-HIV-related mortality in HIV +ve individuals¹⁴

Comorbid condition	Proportion of deaths due to this comorbid disease
Cardiovascular disease	22%
Non-HIV-related cancer	12%
Liver disease	22%
Other	44%

⁹ Kaulich-Bartz J et al. Page 1647

¹⁰ Justice AC. Pages 69-76

¹¹ Justice AC. Pages 69-76

¹² Braithwaite RS et al. Pages 892, 894, 896

¹³ Justice AC. Pages 69-76

¹⁴ Braithwaite RS et al. Pages 892, 894, 896

Yet the spectrum of diseases remains strongly influenced by HIV (see Table 4) due to the virus itself and this again reiterates the importance of early treatment intervention. Non-HIV-related events are influenced by the following ongoing effects of the HIV virus:

- Residual inflammation
- Suboptimal CD4 T cell count gains
- Hypercoagulability resulting from persistent viral replication and expression
- Loss of immune regulatory cells
- Lymphoid fibrosis
- Microbial translocation¹⁵

Table 4: Non-HIV-related disease¹⁶

Immune mechanism	Type of disease
Due to prolonged depletion of CD4 cells	Liver disease
	Malignancies
	Accelerated atherosclerosis
Related to ongoing immune activation	Coronary ischaemia
	Vasculitis
	Pulmonary embolic disease
	Cerebrovascular events

HIV infection: a chronic complex clinical disease

In the past, a clinical focus on CD4 count, HIV RNA and AIDS-defining illness made sense when we had few effective antiretroviral therapies and mortality rates were high. The significant mortality improvement brought about by well tolerated ARTs and a changing epidemiology within resource-rich settings requires a new clinical perspective on the disease, particularly in light of the rise in the proportion of deaths due to non-HIV-related events.

HIV infection and comorbid disease

One study has shown that 65% of individuals infected with HIV aged 50 to 59 have at least one comorbid diagnosis. In

7% of this cohort the comorbid diagnosis qualified as a major medical disease.¹⁷

Comorbid disease results in depleted physiologic reserve with an increased vulnerability to injury. An assessment of this reserve is required as part of the new individualised HIV care approach, particularly in individuals aged 55+. This can be achieved through measuring functional capacity by getting an individual to perform strenuous activity requiring sustained effort.¹⁸

Researchers have suggested evidence-based prognostic non-HIV biomarkers for survival should be measured. These include:

- Haemoglobin (Hb)
- Transaminases (ALT & AST)
- Platelet count
- Serum creatinine
- Hepatitis B & C serology
- History of substance abuse¹⁹



Measure evidence-based prognostic non-HIV biomarkers

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¹⁵ Justice AC. Pages 69-76

¹⁶ Miller S. Slides 2-8; 12-14

¹⁷ Justice AC. Pages 69-76

¹⁸ Justice AC. Pages 69-76

¹⁹ Justice AC. Pages 69-76
Justice AC et al. Pages 148-150

HIV infection: a chronic insurable disease

With an increasing number of deaths in HIV +ve individuals resulting from non-HIV-related events in resource-rich countries, it is reasonable for the life industry to consider that HIV infection no longer represents an uninsurable risk. There is sufficient data from the outcomes of new early HIV intervention to derive extra mortality loadings for HIV-infected individuals which can be applied subject to careful mortality risk assessment.

The European study published in 2013 by Kaulich-Bartz et al, which looked at the insurability of HIV-positive people on ART, noted that most HIV-related mortality occurs during the first few years of ART and that excess mortality rates after 7 years duration of ART are likely to be stable, thereby allowing for extrapolation. Their study showed that HIV-positive individuals with favourable risk profiles could be insurable up to an excess mortality of +400%.²⁰

The central tenets of a risk assessment for HIV-infected individuals should include:

- **Age**
 - At diagnosis
 - At treatment initiation
 - At policy application
- **Immunological status**
 - CD4 T cell count measurement
 - At diagnosis
 - At treatment initiation
 - At policy application
- **Degree of virological suppression**
 - HIV RNA (viral load) measurement
 - At diagnosis
 - At treatment initiation
 - At policy application
- **Pharmacological factors**
 - Medical report from the treating doctor with specific comment on
 - Current and past ARTs
 - Compliance with treatment

- **Comorbidity**
 - History of AIDS-defining illnesses
 - Current comorbid disease
 - History of any current or previous substance abuse
- **Current physiologic reserve**
 - Functional capacity assessment
 - Ability to perform strenuous activity requiring sustained effort (an acceptable insurance industry measure would be a stress electrocardiogram with a minimum attained METS of 7 – 10)
- **Non-HIV biomarkers prognostication**
 - Haemoglobin
 - Transaminases
 - Platelet count
 - Serum creatinine
 - Hepatitis B & C serology

It is reasonable for the life industry to consider that HIV infection no longer represents an uninsurable risk.

Furthermore, there are risk mitigation strategies that some markets have when offering life cover to HIV-infected individuals. These include:

- Term policies
- Capping the policy sum assured

HIV and morbidity cover

Whilst the notion of mortality cover for HIV-infected individuals on ART is becoming increasingly accepted, caution needs to be exercised when considering morbidity cover for this cohort. The reason for this is the evident increase in incidence of non-HIV-related diseases resulting from HIV-induced immune depletion and chronic immune activation. The excess rates required to cover the increased morbidity incidence make such benefits currently unaffordable. The diverse scope of non-AIDS-related diseases also precludes the use of equitable exclusions.

²⁰ Kaulich-Bartz J et al. Page 1647

This may change with the advent of early intervention, although it has also been shown that among HIV-infected individuals initiated on treatment with CD4 T cell counts of ≥ 500 cells/ μ l there remained an increased risk of both Kaposi sarcoma and non-Hodgkins lymphoma compared to HIV-uninfected individuals.²¹

HIV and non-AIDS related cancer

Cancer continues to be a major cause of morbidity in chronic HIV infection treated with ART. Traditional cancer risk factors such as smoking and alcohol use, which have been shown to be more prevalent in HIV-infected individuals, in part explain the higher incidence of cancer seen in this cohort compared to the general population. There is, however, increasing evidence to show that much of the increased cancer incidence risk in chronic HIV infection is due to HIV-induced immunodeficiency and inflammation. Studies have shown that low CD4 T cell counts are independently associated with certain cancers.²²

“HIV is increasingly a disease that people die with rather than die from.”

Braithwaite

Cancers which are known to be due to oncogenic virus infections such as Human Papilloma Virus (HPV) and Hepatitis C Virus (HCV) most likely result from inadequate suppression by an impaired immune system in HIV infection. Another possible mechanism may be a reduced number of circulating cancer surveillance immune cells caused by HIV infection, which can explain the increased incidence of cancers not known to have infectious aetiologies such as lung cancer, colorectal cancer and melanoma.²³

²¹ Silverberg MJ et al. Page 7

²² Silverberg MJ et al. Page 7

²³ Silverberg MJ et al. Page 7

HIV and non-AIDS-related cardiovascular disease

In resource-rich countries, HIV-infected patients on ART have a higher incidence of subclinical structural and functional cardiac abnormalities compared with the general population. Growing evidence suggests that in addition to the traditional cardiovascular risk factors, the increased non-AIDS-related cardiovascular morbidity and mortality in HIV-infected individuals is the result of coronary artery disease due to atherogenesis, endothelial dysfunction and coagulation abnormalities caused by HIV-induced chronic inflammation and immune dysregulation.²⁴

HIV and non-AIDS-related liver disease

End-stage liver disease is a major cause of inpatient admissions and mortality in the era of antiretroviral therapy. The commonest cause of hepatomegaly in HIV-infected individuals is chronic viral hepatitis caused by either Hepatitis B and/or C. Other types of liver disease seen in HIV-infected individuals include non-AIDS-related cancer metastatic liver disease, hepatic steatosis and drug-induced liver injury from antiretroviral medications.²⁵



HIV infection: a chronic insurable disease

²⁴ Cheitlin MD.

Currier JS.

²⁵ Wilcox CM.

Conclusion

AIDS-defining illnesses are becoming less common and are variably associated with outcome. Available, effective and well-tolerated antiretroviral drug therapies along with increasing evidence of the importance of complete viral suppression have resulted in a swing back to early intervention resulting in significant mortality improvements. It is also resulting in an epidemiological shift towards more HIV +ve individuals being aged 50 or older in resource-rich countries.

“HIV is increasingly a disease that people die with rather than die from”²⁶ – and as such should potentially be considered as a life risk that qualifies for life cover. It is therefore important for life industry markets to consider adjusting to the new realities in the field of HIV and they should be encouraged to review existing practices when it comes to insuring HIV-infected individuals in resource-rich settings.



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²⁶ Braithwaite RS et al. Pages 892, 894, 896

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