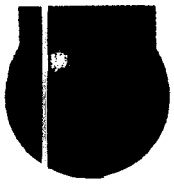

LEADING ARTICLE

The impact of antiretroviral therapy on AIDS and survival

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The impact of antiretroviral therapy (ART) on AIDS and survival has been extensively investigated and reported in the past decade. It is not the intention of this brief commentary to discuss all aspects of this topic, but instead to highlight some recent discoveries along with a look at our own research in this area.

VIROLOGICAL RESPONSE TO ART

Antiretroviral therapy (ART) suppresses the replication of HIV. The three principal factors that determine the level of this suppression in ART-naive patients are the antiviral activity of the chosen ART regimen, the prior rate of viral replication and the adherence to dose scheduling. First, antiviral activity is dependent on the intrinsic efficacy of the individual drugs used in the regimen and the ability of the drug combination to suppress replication of the diverse populations of virus in ART-naive patients [1,2]. Unless all viral populations are inhibited, pre-existing viruses with mutations conferring resistance to the regimen will emerge as the dominant viral population. An example of this is the emergence of virus with K65R mutations when various triple nucleoside/nucleotide reverse transcriptase inhibitors are used [3,4]. Second, it takes more time and is more difficult to suppress viral replication to undetectable levels if the pre-therapy viral levels are high [5]. Finally, treatment only works if it is taken as indicated; if it is not, variable drug pressure will select for viral populations with partial or complete lack of susceptibility to the drugs taken (especially drugs with long half-lives and low genetic barriers to resistance) [6]. In the early stages of treatment, it is usually possible to switch to a regimen that provides enough antiviral activity to suppress viral replication completely [2].

However, it will no longer be possible to suppress viral replication in some patients, despite use of all the currently available antiretrovirals. In many of these patients, although the virus replicates and hence adapts to the selection pressure induced by the virologically failing regimen, viral replication is less aggressive than if the drugs were stopped and the wild-type virus allowed to dominate [7–9]. It is debatable whether the level of virus in patients on ART affects the clinical prognosis independently of the effect the virus has on the immune system (see below) [10,11].

IMMUNOLOGICAL RESPONSE TO ART

Most harm done by HIV infection is caused indirectly by virus-induced immune suppression. The best and most widely used marker of immune suppression is the CD4 cell count, although HIV might also impair other cell types and negatively affect the immune system in other ways [12]. Provision of ART and the subsequent suppression of viral replication relieve the immune system from these effects, improving immune function [13]. CD4 cell counts can continue to rise for up to 6 years after starting ART [14] and the absolute increase in cell count is similar over time, regardless of the severity of immune impairment at initiation of treatment [15].

The immune system recovers quickly if viral suppression is complete [14]. It is possible that distinct drugs affect CD4 cell recovery differently in patients with complete viral suppression [16] and the immune recovery in older patients can be slower [17]. In patients with ongoing ART and viral failure, the CD4 cell recovery rate depends on the viral load [9]. In patients whose viral load is less than 10,000 copies/μl (or more than 1.5 $\log^{10}$ copies/ml below pre-treatment levels) CD4 recovery continues, although at a slower rate than if viral replication were completely suppressed.

SEVERE IMMUNODEFICIENCY BEFORE ART

The association between the most recent CD4 cell count and risk of progression to AIDS or death in untreated patients is an exponential function, with progressively decreasing risk as the count increases above 200 cells/μl [11,18] and an exponentially increasing risk as counts decrease to less than 50 cells/μl [19]. Table 1 shows incidence rates of any death, HIV-related death and development of AIDS in different treatment eras, stratified by CD4 cell count. The incidence of AIDS, death and HIV-related death has dropped substantially from the pre-ART era to the late ART era, even among patients with similar levels of immunodeficiency. The incidence of AIDS is between 25% and 50% of the pre-ART level, even when the CD4 cell count increases that occur among patients starting therapy are taken into account. Starting ART clearly reduces the risk of AIDS or death, regardless of the current level of immunosuppression. However, the greatest benefit is seen in patients whose risk of AIDS or death is highest, when small increases in CD4 cell count can substantially reduce these risks.

It takes time for the immune system to recover; therefore, patients starting ART with low CD4 cell counts remain at risk of AIDS or death in the months after initiating ART [5]. In addition, disease that developed before starting ART might influence the prognosis after treatment is initiated. Consequently, death or the development of AIDS in patients who had low CD4 cell counts at therapy initiation might reflect opportunistic infections (OIs) that were

Table 1: Incidence per 100 person-years of follow-up (95% confidence interval) of AIDS, all deaths and HIV-related deaths according to treatment era and latest CD4 count [9]. vs, versus.

Latest CD4 count	Pre-ART (1994–1995) 1	Early ART (1996–1997) 2	Late ART (1998–2002) 3	Test for trend P value 1 vs 2 vs 3	Test for trend P value 2 vs 3
All deaths					
≤20	68.9 (62.8–75.0)	80.0 (71.5–88.5)	34.6 (28.6–40.6)	<0.0001	<0.0001
21–50	32.2 (26.9–37.5)	28.1 (22.7–33.5)	25.7 (20.5–30.9)	0.0083	0.52
51–100	21.1 (16.7–25.5)	9.5 (7.1–11.9)	8.3 (6.3–10.3)	<0.0001	0.44
101–200	5.9 (4.2–7.6)	4.0 (3.0–5.0)	4.0 (3.3–4.7)	0.046	0.95
201–350	2.7 (1.7–3.7)	1.4 (0.9–1.5)	1.4 (1.1–1.7)	0.013	0.89
>350	1.4 (0.6–2.5)	1.2 (0.7–1.8)	0.7 (0.6–0.8)	0.008	0.041
Total	19.0 (17.7–20.3)	9.3 (8.6–10.0)	2.6 (2.4–2.8)	<0.0001	<0.0001
HIV-related deaths					
≤20	53.8 (48.4–59.2)	66.8 (59.1–74.6)	26.2 (20.9–31.4)	<0.0001	<0.0001
21–50	22.9 (18.4–27.4)	21.6 (16.8–26.3)	11.9 (8.4–15.4)	<0.0001	0.002
51–100	16.0 (12.2–19.9)	7.3 (5.2–9.3)	5.5 (3.9–7.2)	<0.0001	0.19
101–200	4.7 (3.2–6.2)	2.5 (1.7–3.3)	2.2 (1.7–2.8)	<0.0001	0.54
201–350	1.8 (1.1–2.7)	1.2 (0.7–1.7)	0.8 (0.5–1.0)	<0.0001	0.048
>350	0.9 (0.4–2.0)	1.0 (0.5–1.6)	0.4 (0.3–0.5)	<0.0001	<0.0001
Total	14.6 (13.4–15.8)	7.4 (6.8–8.1)	1.5 (1.4–1.7)	<0.0001	<0.0001
AIDS					
≤20	97.9 (88.6–107.2)	103.2 (91.5–114.9)	50.4 (41.5–59.3)	<0.0001	<0.0001
21–50	64.8 (56.0–73.6)	52.7 (44.2–61.2)	23.4 (18.0–28.8)	<0.0001	<0.0001
51–100	42.4 (35.5–49.3)	24.7 (20.6–28.3)	10.5 (8.1–12.9)	<0.0001	<0.0001
101–200	15.9 (13.0–18.8)	7.6 (6.2–9.0)	4.3 (3.5–5.1)	<0.0001	<0.0001
201–350	6.1 (4.6–7.6)	3.8 (2.9–4.7)	1.5 (1.2–1.8)	<0.0001	<0.0001
>350	3.6 (2.2–5.0)	2.6 (1.8–3.4)	0.7 (0.5–0.9)	<0.0001	<0.0001
Total	27.4 (25.7–29.1)	13.4 (12.5–14.3)	2.6 (2.4–2.8)	<0.0001	<0.0001

diagnosed before starting ART or indicate that treatment was initiated late in the course of HIV infection. Death or the development of AIDS in these circumstances does not imply that ART has an adverse effect or is ineffective.

Disease prevention by ART

There is evidence that all types of OI can be prevented by the provision of ART. However, recent findings suggest that several diseases that were not thought to be influenced by immune status are also affected. For example, both liver disease associated with chronic viral hepatitis infection and the development of non-AIDS-defining malignancies seem to be negatively affected by immune suppression. Recent results from the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) [20] and Strategies for Management of Anti-Retroviral Therapy (SMART) studies [21] suggest that ART reduces the risk of developing these diseases and this is primarily due to increases in CD4 cell count.

Another example of ART preventing other disease is seen with hepatitis B, viral replication of which is inhibited by three commonly used anti-HIV drugs: lamivudine (3TC), emtricitabine (FTC) and tenofovir (TDF) [22]. These drugs select for hepatitis B virus with drug resistance mutations more slowly than they select for such mutations in HIV, although the rate is substantially higher for 3TC and FTC[23]. Finally, reduction of viral replication by 3TC probably leads to a reduced risk of liver-related death [24].

Benefits and risks of ART

ART is associated with a >80% reduction in the risk of AIDS or death. Before the introduction of ART, the incidence of new AIDS or death across Europe was in excess of 40 per 100 patient-years of follow-up (PYFU). That is, before the introduction of ART, for every 100 patients followed for 1 year, 40 would develop AIDS or die by the end of that year. Currently, this rate is less than 4 per 100 PYFU [19]. Few areas of medicine have seen such impressive improvements in prognosis over such a short time span.

However, ART is also associated with undesirable effects, which can be categorised into three main groups: early onset adverse effects, late onset adverse effects and unintended side effects from the immunological recovery induced by ART. The early onset adverse effects, such as hypersensitivity reactions and gastrointestinal symptoms, are typically restricted to one organ system and are induced by only one drug. Conversely, the late-onset adverse effects usually develop indirectly by initial subclinical alterations of the metabolism. The most concerning example is the progression of cardiovascular disease (CVD), as this will augment the exponential age-related increase in risk of death from CVD [25]. Adverse outcomes from immunological recovery are collectively known as immune reconstitution inflammatory syndrome (IRIS). However, IRIS is mainly seen in patients who had low CD4 cell counts before commencing ART and can therefore be avoided with earlier initiation in the course of chronic infection [26].

When to start and structured treatment interruptions

It is outside the scope of this article to outline fully the arguments required to provide a balanced view on the much debated question of when to start treatment [27]. Recent reports remind us that patients living with CD4 counts in the range of 200–350 cells/μl are at increased risk of OIs and death [18,21]. Therefore, it can be argued that ART should be initiated before these levels are reached.

Recent data from the SMART study [21] suggested that structured treatment interruptions (STIs) (the duration of which were determined by the rate of CD4 count deterioration to 200–250 cells/μl) were associated with an excessive risk of OIs. Although most patients with STIs had CD4 counts above 200 cells/μl, they had consistently lower counts and higher levels of viral load than patients who had continuous treatment. This suggests that, although STI patients had CD4 cell counts above the threshold at which the risk of OIs and death was lowest, there was an increased risk caused by having lower CD4 cell counts than the patients who had continuous treatment.

The SMART study also showed that risk of death from causes other than OIs was increased in patients who had STIs, as was the incidence of non-fatal CVD, liver disease and renal disease. Therefore, interruption of ART is not recommended.

Conclusions

Currently, ART can reduce viral replication but not eradicate infection. Consequently, any strategy for using ART should consider how to enable life-long adherence. The parameters that will determine this are the future drug options, which are affected by dose-limiting toxicities, and the presence of archived or circulating virus with various types of drug resistance mutations

For most patients with full access to care, there is an array of future drug options. However, the capacity for innovation in drug discovery and the development of new drugs will be key determinants in ensuring that a wide range of drugs continues to be available. One key future focus of academic research will be to explore the underlying mechanisms that lead to the reduction in future drug options for individual patients. This can be done by challenging current drug strategies, with the resultant improvement in evidence-based patient management.

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