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Andrew N Phillips, Brian G Gazzard, Nathan Clumeck, Marcelo H Losso and Jens D Lundgren

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When should antiretroviral therapy for HIV be started?

Treatments for HIV have advanced rapidly over the past decade. Andrew Phillips and colleagues argue that we should re-evaluate the timing of treatment in the light of new knowledge

Opinions on when patients with HIV should start antiretroviral therapy have differed widely.¹⁻⁴ A definitive answer has proved elusive in the absence of a randomised trial. Treatment guidelines have cited data from observational cohorts and have generally concluded that treatment should first be considered as the CD4 count falls below $350 \times 10^6/l$, less than half of the average normal concentration in uninfected people,⁵ but certainly started before the level has reached $200 \times 10^6/l$.^{6,7} Recent research means that we should re-evaluate whether this position remains justified. Before doing this it is important to be clear on the reasons for reaching the position in the first place.

Why have we delayed treatment?

Antiretroviral therapy clearly reduces the risk of AIDS related diseases, even in those with a relatively high CD4 count. A large joint cohort analysis shows a decreased rate of AIDS after starting antiretroviral therapy, even in those with CD4 counts above $350 \times 10^6/l$ (fig 1).⁸ So what have been the reasons for delaying?

Firstly, many antiretroviral drugs are inconvenient to take and are associated with unpleasant effects including nausea, diarrhoea, headache, and central nervous system toxicity. They may also cause occasional life threatening adverse effects such as hypersensitivity reactions, acute hepatitis, lactic acidosis, and pancreatitis.⁹ Furthermore, long term use of antiretroviral therapy has been linked with increased risk of myocardial infarction.¹⁰ If therapy can safely be delayed most patients would prefer to wait.

Secondly, the absolute risk of AIDS related diseases has been felt to be sufficiently low at CD4 counts above $250 \times 10^6/l$ that delay can be considered, given the disadvantages of treatment. Tables that provide

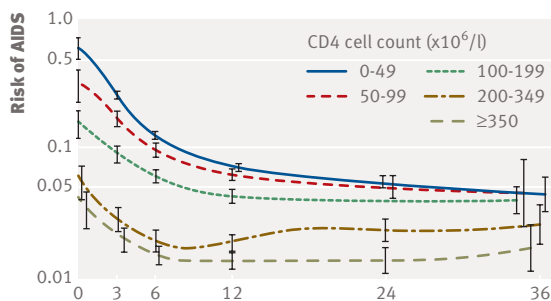


Fig 1 | Risk of AIDS over time according to CD4 count at start of antiretroviral therapy. Adapted from Egger *et al*⁸

Andrew N Phillips

professor of epidemiology, Department of Primary Care and Population Sciences, Royal Free and University College Medical School, London NW3 2PF

Brian G Gazzard

research director, HIV and genitourinary medicine, Chelsea and Westminster Hospital, London

Nathan Clumeck

professor, Department of Infectious Diseases, Hospital St Pierre, Brussels, Belgium

Marcelo H Losso

head, Servicio Inmunocomprometidos, Hospital J M Ramos Mejía, Buenos Aires, Argentina

Jens D Lundgren

professor of infectious disease epidemiology, Copenhagen HIV Programme, Hvidovre Hospital, Copenhagen, Denmark
Correspondence to: A N Phillips a.phillips@pcps.ucl.ac.uk

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the six month risk of AIDS for a person with a given CD4 count, viral load, and age^{6,11} indicate that a 35 year old with CD4 count $350 \times 10^6/l$ and viral load 30 000 copies/ml has an estimated 1.6% risk of an AIDS disease, for example.¹¹ While this risk would be reduced by antiretroviral therapy, many clinicians and patients have not considered it sufficiently high to warrant initiation of therapy.

Thirdly, treatment of HIV has developed rapidly over the past 15-20 years. Patients' responses to antiretroviral therapy have improved,¹²⁻¹⁴ partly because of better adherence as a result of reduced toxicity, more convenient regimens, and adherence support. Furthermore, drugs with longer half lives that are more forgiving of poor adherence have become available. Understanding of resistance has also improved, as has the availability of drugs to use when extensive resistance is present.

Given this ongoing improvement it has made sense to delay antiretroviral therapy. For example, a patient starting therapy in 1996 might have been put on a regimen containing either full dose zidovudine (associated with severe gastrointestinal adverse effects) or hard gel zalcitabine (associated with a high rate of resistance). If he or she had been able to wait until 1999 then a regimen of zidovudine and zalcitabine could have been started, which has proved durable success and is still widely used. In addition, it was feared that starting antiretroviral therapy too early could lead to premature exhaustion of all available treatment options because of resistance.

What has changed?

Estimates of the risks of developing AIDS have not changed,¹¹ but the context in which we are weighing up the risk has altered. We have started to appreciate, albeit with experience only of relatively short term use, that antiretroviral therapy may permit close to a normal lifespan. Given this perspective, the 1.6% six month risk of AIDS for a person with CD4 count $350 \times 10^6/l$ and viral load of 30 000 copies/ml discussed above begins to not look so low. Further reminder of the risks at CD4 counts above $200-250 \times 10^6/l$ has come from recent results of the strategies for management of antiretroviral therapy (SMART) study (box 1). This compared episodic antiretroviral therapy guided by CD4 count with continuous antiretroviral therapy and found a significantly increased risk of disease progression in those on episodic therapy despite the fact that almost all participants had CD4 counts above $200 \times 10^6/l$ throughout the trial.¹⁵ Cohort studies have also shown a continuum

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of decreased risk with higher CD4 counts, even in the 200-500×10⁶/l range, in patients who both have and have not received antiretroviral therapy.^{11 16}

Our understanding of drug toxicities has also improved recently. The increased risk of myocardial infarction with antiretroviral therapy is now better understood and seems to be associated with protease inhibitors not non-nucleoside reverse transcriptase inhibitors and is at least partly related to lipid changes with these regimens.¹⁷ As such, the threat can be better managed clinically in individual patients. Similarly, lipodystrophy has been a major concern and reason for delaying antiretroviral therapy.^{18 19} The lipodystrophy component, for example, is now known to be related to thymidine analogues^{19 20} and can thus be better avoided. In addition, the SMART trial unexpectedly showed that patients who had interrupted antiretroviral therapy had significantly increased risk of a combined endpoint of myocardial infarction, stroke, liver cirrhosis, and renal failure compared with those on continuous treatment.¹⁶ It had been hypothesised that reduced use of antiretroviral therapy would lower the risk of such conditions. Furthermore, recent findings from the data collection on adverse event of anti-HIV drugs (DAD) study have shown that risk of death from liver disease and of “non-AIDS” cancers are increased at lower CD4 counts, with differences even between those in the 200-350×10⁶/l and >350×10⁶/l categories.²¹ SMART also confirms that differences in CD4 count within this range translate into differences in risk of deaths from what had been thought of as non-HIV related causes. Finally, in SMART interrupted therapy had no benefits on quality of life.²²

The third reason for delaying was to wait for improvements in drugs and adherence support. Again, recent

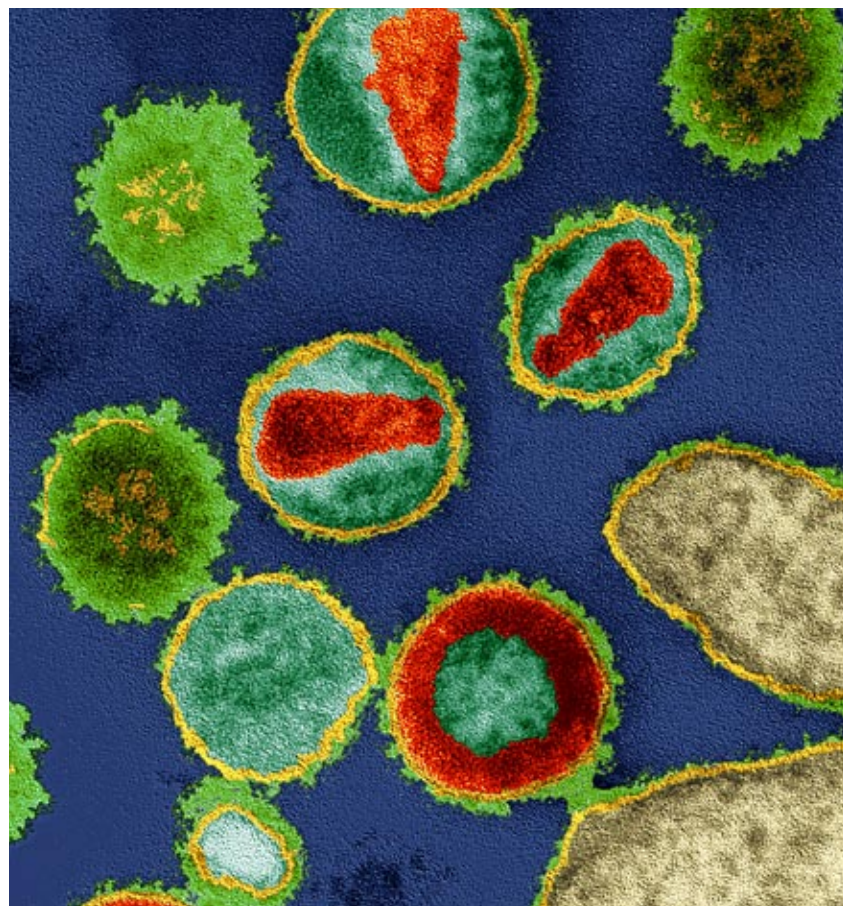


Fig 2 | HIV: when should antiretroviral therapy be started?

Box 1 | Strategies for management of antiretroviral therapy (SMART) trial¹⁵

The trial enrolled 5472 patients with HIV infection and CD4 count >350×10⁶/l from 33 countries. Most were taking antiretroviral drugs

Episodic, CD4 count-guided treatment was compared with continuous treatment. In the episodic arm treatment was started when the CD4 count was below 250×10⁶/l and stopped when it rose above 350×10⁶/l

The planned follow-up was 6-9 years, but the data and safety monitoring board recommended stopping recruitment after an average 16 months' follow-up

The risk of AIDS diseases and death was significantly higher in those in the episodic arm

Diseases not typically associated with immunodeficiency or traditionally defined as AIDS related (such as cardiovascular, kidney, or liver disease) also occurred at a significantly increased rate in the episodic arm compared with the continuous arm

data have weakened this argument for delay. Recent cohort analyses have shown that the initial response to antiretroviral therapy has improved substantially and now tends towards a plateau.¹²⁻¹⁴ Viral load responses are now generally so good that there may be relatively little scope for further improvement. In one study, the percentage of patients with initial virological failure dropped from 23% in 1996 to 8% in 2002.¹²

A related reason for delaying antiretroviral therapy was the concern over accumulation of drug resistance and exhaustion of drug options. Although we observe an appreciable rate of appearance of resistance mutations over time among patients taking antiretroviral therapy, the rate of accumulation of resistance to the three main classes seems slow.²³ Even if one or two regimens have failed, new drugs are likely to become available soon that are active against a virus which is resistant to current drugs.²⁴

Treatment decisions

In the light of this re-evaluation, when should a patient start antiretroviral therapy? Delaying treatment until

Box 2 Considerations for trial in patients with CD4 count $>500 \times 10^6/l$ comparing immediate antiretroviral therapy versus deferral until count is $350 \times 10^6/l$

- Risk of AIDS in untreated patients with CD4 count $>350 \times 10^6/l$ is appreciable. SMART and other studies also suggest a raised risk of other serious conditions not previously thought to be related to HIV
- Since reasons for delaying therapy are now much weaker, earlier use of antiretroviral therapy should be evaluated
- Antiretroviral therapy has been changing rapidly over the past 10-15 years, making a long term trial unfeasible. Therapy is now more stable and durably successful and could be evaluated over longer periods
- The trial would need to be global and follow several thousand patients for at least 5 years
- The cost effectiveness of starting antiretroviral therapy in patients with CD4 counts $>500 \times 10^6/l$ is unknown until a trial is done, but it is likely to be at least as great as the cost effectiveness of continuing treatment in patients with counts $>500 \times 10^6/l$

the CD4 count has fallen below $300-350 \times 10^6/l$ carries risks that it seems clear will not be balanced or outweighed by any short or longer term mortality risks from immediate therapy. We therefore suggest that guidelines should now recommend starting treatment at around $350 \times 10^6/l$, so long as the patient is ready. For patients with higher CD4 counts the risk-benefit balance remains uncertain, and we need an international randomised trial in patients with a CD4 count above $500 \times 10^6/l$ comparing immediate treatment with deferral of treatment until the count reaches $350 \times 10^6/l$. The increased stability of HIV treatment now makes such a trial possible and would enable us to evaluate the risk of non-AIDS related diseases, which SMART suggested might also be increased in those not taking antiretroviral treatment, as well as of the risk of developing AIDS (box 2).

Treatment, of course, depends on availability of the drugs. Patients and doctors in settings where the newer less toxic and more convenient regimens are not an option may still prefer to carry the risks and wait until these become available. In settings where antiretroviral therapy availability is severely limited, the priority for initiation should continue to be those with the greatest level of immunodeficiency, where the clinical benefits are greatest.

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SUMMARY POINTS

Policy on when to start antiretroviral therapy for HIV has been based on inference from observational studies rather than randomised trials

Treatment has generally been delayed until counts reach $200 \times 10^6/l$ because the low risk of AIDS was outweighed by the toxicity and inconvenience of drugs, fear of rapid resistance accumulation, and likelihood of further improvements in antiretroviral drugs

Recent evidence indicates that the reasons for delaying therapy have weakened considerably

Evidence suggests patients would benefit from treatment at CD4 counts of no lower than $350 \times 10^6/l$

A randomised trial is needed to evaluate the risks and benefits of treatment at counts above $500 \times 10^6/l$

Contributors and sources: All authors have worked in HIV infection for many years and are involved in design, coordination, and analysis of large randomised trials and observational studies of people with HIV. BGG is chair of the British HIV Association treatment guidelines committee, which ANP was also a member of. NC and JDL are members of the executive committee of the European AIDS Clinical Society.

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