When and why to start antiretroviral therapy?

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The question about when to start antiretroviral therapy in HIV-1-infected patients has been debated since the discovery of the first antiretroviral agent (zidovudine) back in 1986 and has been fuelled by the introduction of highly active combined antiretroviral therapy (cART) 10 years later in 1996. The dramatic improvement in the mortality rate associated with cART supported the principle of ‘hitting early and hard’, but the initial enthusiasm was quickly tempered by the realization of the inconveniences and the short- to mid-term treatment-related toxicities, including lipodystrophy. In 2009, cART can be very simple and generally well tolerated. All patients with a CD4+ T cell count of <350 cells/mm³ should receive cART. Moreover, several cohort studies have convincingly demonstrated a significant reduction of AIDS- and non-AIDS-related events when cART is initiated at >350 CD4+ T lymphocytes/mm³, and even at >500 CD4+ T lymphocytes/mm³. Also, cART may be considered when there are associated co-morbidities, such as hepatitis C. In addition to individual benefits, an undetectable viral load in response to cART is associated with a substantial reduction in the likelihood of HIV transmission. This can benefit seronegative sexual partners and can potentially diminish the number of new infections, especially if those infected persons unaware of their situation can be identified and advised to initiate CART. Willingness to be treated and to adhere to the prescribed medication still remains the key to success.

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In those settings where cost is not a major limiting factor, the real question is why we do not recommend combination antiretroviral therapy (cART) for all HIV-1-infected patients immediately after diagnosis. Primary HIV-1 infection is rarely identified early enough, due to lack or misinterpretation of clinical manifestations.1 About 3–6 months later, the plasma viral load reaches the setpoint (usually somewhere between 10⁵ and 10⁶ HIV-1 RNA copies/mL),2 reflecting a dynamic equilibrium between the capability of the immune system to control the viral replication and the ability of the virus to evade it.3 The direct and indirect consequence of this ‘uncontrolled’ viral replication is a progressive drop of the peripheral blood CD4+ T lymphocyte count, by an average of 50–100 cells/mm³ per year.4 cART can very quickly (usually in <3–6 months) and efficiently suppress the HIV-1 replication,3 establishing a new setpoint at <50 copies/mL and usually as low as ~1–3 copies/mL when single-copy assays are used to measure the plasma viral load.5–10

Moreover, in 2009, the initial cART can be very simple, convenient and well tolerated (at least at short- to mid-term), and with almost a 100% response rate among patients with good adherence to the prescribed medication.11–13 As a consequence, the peripheral blood CD4+ cell count will not only stop dropping, but will recover, at least partially.14,15 Lastly, the rate of AIDS- and non-AIDS-related events and mortality will be dramatically reduced.16–23 Yet, until very recently, most guidelines24–28 only recommended the initiation of cART when the CD4+ cell count dropped below as low as 200 CD4+ T cells/mm³. The main reasons were: (i) the inconveniences associated with very complicated treatment schedules that must be maintained for life;29 (ii) the short- to mid-term toxicity (e.g. lipodystrophy);30–33 and (iii) the relatively low rate of classical AIDS-related events when the CD4+ cell count remains >200 CD4+ cells/mm³, even in the absence of cART.34 Despite such a conservative approach, the life expectancy significantly increased,35 but still remained below that of the general population after adjusting for age, sex and geographical area.36 To close this gap we may need to completely normalize the CD4+ cell count (>500–600 cells/mm³),37 and this level is rarely achieved when cART is initiated at <200 CD4+ cells/mm³ and in <50% of patients when cART is initiated at between 200 and 350 CD4+ cells/mm³.38 In addition, cohort studies,39 and at least one randomized study,38,39 have clearly demonstrated that viral replication ‘per se’ is harmful, irrespective of the CD4+ cell strata, leading to what we now call non-AIDS events and non-AIDS mortality.21,38 Among the list of non-AIDS events, we can underline cardiovascular complications, a higher than expected rate of some malignancies, faster evolution of hepatitis C and B co-infections, HIV-1-associated nephropathy, and, possibly, premature ageing and frailty.38,39 Lastly, the risk of lipodystrophy has been minimized by avoiding the utilization of thymidine analogues32 and also by the introduction of more ‘lipid friendly’ antiretrovirals.30

All patients with <350 CD4+ T cells/mm³ should receive cART. Recommendations to start cART at >350 CD4+ cells/mm³ are...
already considered in most widely used international and national guidelines in the Western world, based on several cohort studies and also on a subanalysis of the antiretroviral ‘naive’ or untreated patients randomized in the SMART study, mainly when co-morbidities like hepatitis C are present. Furthermore, a reduction in the overall mortality of ~90% has been found in a US multicohort study when cART was initiated at >500 CD4+ cells/mm³, as opposed to initiation below that point. In practice, a recommendation to treat patients at >500 CD4+ cells/mm³ would mean a general recommendation to treat almost everybody from the moment of diagnosis, unless a formal contraindication or unwillingness of the patient exists. The hypothesis of initiating cART at >500 CD4+ cells/mm³, as opposed to deferring until the CD4+ cell count drops to <350 cells/mm³, will be explored in an ongoing randomized study (the START study) that may face recruitment problems in the Western world if standard practice moves to immediate treatment.

In addition to the benefits for the patients themselves, early initiation of cART and reducing the plasma viral load below the quantification limit have benefits for the patients’ uninfected sexual partners and may be an overall preventive strategy when combined with other more conventional preventive strategies. The reason is that despite unprotected sex, HIV-1 transmission is minimized when plasma viral load remains below the limit of quantification. Direct costs associated with an earlier initiation of cART may increase in the short-term; however, considering that almost all (if not all) patients will require cART for life sooner rather than later, the direct cost reduction at 20-30 years associated with a deferral of treatment is almost negligible.

The drawbacks (or the problems to be solved) to implementing the early initiation of cART are the ‘late presenters’ and the low-/middle-income countries, where >90% of HIV-1-infected patients live and many of them actually die due to AIDS-defining events, as opposed to the non-AIDS events and non-AIDS mortality that are more frequent in rich countries. However, even in rich countries the percentage of late presenters (defined as presentation with <350 CD4+ cells/mm³ or with AIDS events) is not lower than 50%–70% and this figure has remained relatively stable during the past 5–10 years. Lastly, despite substantial improvements in the access to cART in the developing world, the reality was that by the end of 2008, >6 million persons were not receiving cART, despite a CD4+ cell count of <200 cells/mm³ or having already developed an AIDS event. Moreover, those already on treatment are frequently receiving relatively toxic drugs almost no longer in use in the Western world.

In summary, during recent years, substantial evidence has emerged in favour of a very early initiation of cART, in particular among those patients with co-morbidities such as a pre-existing relatively high cardiovascular risk, a hepatitis C or B co-infection, or with a serodiscordant sexual partner, as well as among women with a desire or planning to get pregnant. We should plan for a success rate of >90% at 1 year and a sustained response over time. This goal can be achieved with several different combinations, all of them being relatively simple, convenient and well tolerated short- to mid-term. However, a high level of adherence to the prescribed medication still remains a crucial component of success. Consequently, unless the CD4+ cell count is very low, it might be better to defer the initiation of cART if the patient is not fully committed to comply with a lifelong treatment. The potential eradication of HIV-1 still remains in the domain of fundamental research.

**Transparency declarations**

None to declare.

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