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# Antiretroviral therapy of late presenters with advanced HIV disease

## Manuel Battegay*, Jan Fehr, Ursula Flückiger and Luigia Elzi

*Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland*

**Potent antiretroviral therapy (ART) has dramatically improved the prognosis of HIV-1-infected individuals. However, 10% to 30% of patients in Western countries still present late for care, when CD4 T cells are below 200 cells/mm$^3$ and symptomatic HIV disease has occurred. Clinical considerations for advanced HIV disease are paramount as morbidity and mortality are directly correlated with a low initial CD4 T cell count, which is commonly associated with the simultaneous occurrence of co-morbidities, particularly opportunistic infections. Upon start of ART, the clinical entity of immune reconstitution inflammatory syndrome may occur and, in this context, raise the question of early versus delayed ART in patients treated for opportunistic infections. Recent data clearly indicate that an earlier start of ART is warranted in this latter situation. Guidelines for specific antiretroviral treatment for late-presenting patients are lacking. Knowledge about drug–drug interactions and co-morbidities should guide treatment choices and influence the clinical management and monitoring of drug-related side effects and interactions. Importantly, the outlook of patients who present late is very much dependent upon the initial response to ART. Nevertheless, even if optimal response to treatment has been achieved, long-term prognosis may be impaired in patients who initially presented with advanced HIV disease. We encourage physicians to perform HIV testing more frequently in order to detect HIV-infected individuals in time.**

Keywords: IRIS, HIV-test, CD4 cell count, tuberculosis

## Introduction

Combination antiretroviral therapy (ART) has dramatically improved the prognosis of HIV-1 infected individuals.[1–3] However, 10% to 30% of patients still present late for care, when severe immunosuppression has already developed.

The natural course of HIV-1 infection is characterized by a progressive loss of CD4 T cells leading to severe immunodeficiency. A decrease in CD4 T cells below 200 cells/mm$^3$ is the threshold where the risk of opportunistic infections dramatically increases. Therefore, current management of HIV infection aims to prevent opportunistic infections and to reduce mortality by starting ART before CD4 T cells decline below this critical level.[4] The advent of dual ART resulted in a decrease in mortality of 30% to 50% in the early 1990s (Table 1),[5–7] followed by an even more dramatic improvement of prognosis with the introduction of triple combination ART in the mid-1990s.[1,7–12] However, HIV-infected patients continue to die from both HIV-related and non-HIV-related causes. The residual morbidity and mortality in HIV-infected patients are mainly due to the following reasons: (i) late presentation for HIV care with delayed uptake of ART;[13] (ii) age-related and CD4-independent morbidity due to concomitant diseases (in particular cardiovascular diseases, hepatitis C with liver failure, and malignancies);[14,15] and (iii) suboptimal treatment because of multidrug-resistant viral strains and lack of treatment options.[16] Although the first two factors are the predominant causes of death in HIV-infected individuals, the prevalence of HIV resistance to all currently available drug classes has recently decreased, reflecting the important advances in this field. Owing to the development of new drugs and drug classes, 50% to 70% of patients with highly resistant HIV and triple class failure achieve optimal response to ART with virological suppression below the limit of detection (HIV-RNA <50 copies/mL)[17,18] and immunological recovery.

## Scale of late presentation

Late and very late presentation of HIV-infected individuals may be defined if CD4 T cell count at presentation for care is below 200 and 50 cells/mm$^3$, respectively, or if an AIDS-defining condition has already occurred. However, these definitions may shift as more recent guidelines have recommended an earlier start of therapy, i.e. once CD4 T cells drop below 350 cells/mm$^3$.[4] Moreover, there is increasing evidence that initiation of ART at a higher CD4 T cell count of between 350 and 500 cells/mm$^3$

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*Corresponding author. Tel: +41-61-265-50-72; Fax: +41-61-265-31-98; E-mail: mbattegay@uhbs.ch

**Table 1.** ART dramatically decreased mortality

| Year | Study | Design | | Decrease in mortality (%) |
|---|---|---|---|---|
| 1997 | Delta[5] | RCT | ZDV versus dual ART | 30–50 |
| 1997 | ACTG 175[7] | RCT | ZDV versus dual ART | 30–50 |
| 1997 | ACTG 320[8] | RCT | dual versus HAART | 70–80 |
| 1997 | SHCS[1] | OS | no HAART versus HAART | 70–80 |
| 1998 | HOPS[9] | OS | no HAART versus HAART | 70–80 |
| 2003 | EUROSIDA[10] | OS | 1996–97 HAART versus 1998–2002 HAART | 86 |
| 2005 | SHCS[11] | OS | no HAART versus HAART | 86 |
| 2007 | Danish cohort[12] | OS | HIV versus non-HIV | ∼10–38 years of life prolongation after start of ART normal life expectancy (?) |

RCT, randomized controlled trial; OS, observational study; ZDV, zidovudine; HAART, highly active antiretroviral therapy.

may be associated with a better prognosis of both HIV and non-HIV-related conditions such as viral hepatitis C and malignancies.[4] Thus, late presentation might strongly affect overall prognosis of HIV-infected individuals.

In the Western world, 10% to 30% of HIV-infected individuals are reported to present late for care.[13,19] This proportion is clearly higher in developing countries, particularly in sub-Saharan Africa, South-East Asia and South America, because of the limited access to healthcare and HIV treatment.[20,21] Impressively, the median CD4 T cell count at starting ART across all regions worldwide except Australia was reported to be below 200 CD4 T cells/mm$^3$ in the years 2003–05.[22] The clinical significance of late presentation was also examined in a large cohort study in Switzerland, where 30% and 10% of patients attended clinical care late and very late (i.e. with CD4 T cells <200 and <50 cells/mm$^3$), respectively.[23] In this study, late initiation of ART was predominantly due to late presentation and not to delayed uptake of ART, as patients entering the Swiss HIV Cohort Study promptly started ART. Risk factors of late presentation were older age, heterosexual HIV transmission risk and non-white ethnicity, similar to previous studies.[13,24]

In view of the marked differences in mortality when comparing late presenting individuals with those presenting earlier, and the prolonged risk of HIV transmission, prevention of late presentation by expanded HIV-testing and reduction of organizational, psychosocial and educational barriers is a priority.

## Clinical considerations for advanced disease

Clinical considerations and evaluation of late-presenting HIV-infected individuals and advanced HIV disease include history of previous opportunistic infections, HIV-associated symptoms, for example, weight loss, diarrhoea, fatigue and concomitant diseases (particularly co-infection with viral hepatitis B and/or C; psychiatric disorders and active substance abuse), which could complicate ART or negatively influence adherence to ART. In the physical examination, subtle clinical signs might give an indication of mild-to-moderate immunodeficiency, e.g. oral candidiasis or oral hairy leukoplakia; for further details, see review by Battegay *et al.*[25] More importantly, the diagnostic approach in a patient recently starting ART who develops new

symptoms is very challenging. E.g. fever, in particular low-grade fever, might be due to: (i) HIV directly (very high viral loads); (ii) HIV-related complications such as opportunistic infections; (iii) immune reconstitution inflammatory syndrome (IRIS) after initiation of ART; (iv) drug-related complications (through treatment of opportunistic infections or ART); (v) concurrent unrelated complications, for example, catheter-related infections; or (vi) other diseases.

In addition to symptoms and signs of advanced HIV disease, late presentation has particular features in conjunction with IRIS after the initiation of ART. Figure 1 illustrates the possible pathophysiology of IRIS.[26–28] Fever and enlarged lymph nodes are typical clinical signs of excessive inflammatory response. Importantly, such specific reactions are crucial for the
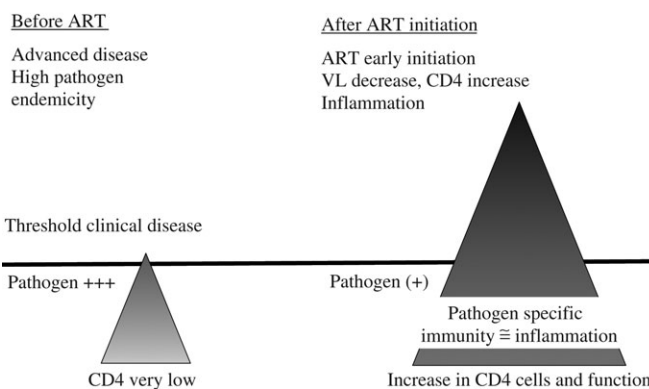


**Figure 1.** Advanced HIV disease with low CD4 T cells count and high pathogen endemicity are well-known risk factors for IRIS. Due to very low CD4 T cell counts, CD4- and/or CD8-mediated cellular immune responses are likely to be strongly impaired and defence inflammatory reactions may not develop. Consequently, the threshold for clinically manifested disease is not crossed. Following ART initiation, viral load rapidly decreases and cellular immune functions improve within days or weeks, leading to an increased pathogen-specific immunity, which becomes apparent as an inflammatory reaction. Of course, such a reaction is recognizable only if a pathogen is present.

elimination of opportunistic infections, and later for stopping primary or secondary prophylaxis for such pathogens. However, in rare cases, IRIS may lead to severe complications including death. Importantly, data from recent studies clearly indicate that early combination ART is advantageous when opportunistic infections are present, as the overall mortality is excessively high in patients presenting with very late HIV disease and opportunistic infections.[27–29] It has been shown that delaying combination ART is associated with increased mortality.[29] Also, IRIS can be managed with close monitoring and symptomatic treatment including steroids.[29,30] Management of late presenters with tuberculosis is particularly challenging because of the high risk of developing IRIS, estimated at up to 32% in association with low CD4 T cell count at baseline and early ART initiation,[30] additive drug toxicity and interactions resulting from antimyco-bacterial therapy. In case of active tuberculosis at presentation, immediate antituberculous treatment should be started and ART should not be postponed by more than 4–8 weeks. However, ART may be initiated even earlier if the CD4 T cell count is very low ($<$50 cells/mm$^3$) as HIV-related mortality is very high in this circumstance. If reactivation of tuberculosis becomes clinically apparent during ART (i.e. IRIS), it is possible to continue ART because IRIS is usually not life-threatening.[30]

## ART for late presenters

Is there a specific initial ART regimen for late presenters? The simplest answer would be no. However, several aspects which also apply for the earlier initiation of treatment should be considered before starting ART in late presenters. First, the presence of transmitted HIV drug resistance, which may occur in 5% to 25% of patients and predominantly refers to non-nucleoside reverse transcriptase inhibitors (NNRTIs),[31] should be investigated. Secondly, factors that may influence clinical management and require close monitoring of drug-related side effects and drug interactions, such as co-infection with viral hepatitis B and/or C and concomitant treatment of opportunistic infections, should be evaluated. Thirdly, the presence of psychiatric disorders, active drug use or socioeconomic barriers, which may negatively affect adherence and therefore efficacy of treatment, should be assessed.

The question of whether boosted protease inhibitors (PIs) or NNRTIs should be chosen as a third drug is also difficult to answer. A large meta-analysis of 53 trials including 14 264 patients indicated that these two drug classes are of equitable potency, as measured by the percentage of virological suppression (HIV-RNA below 50 copies/mL) achieved at 48 weeks after starting treatment.[32] Similarly, no difference in the immunological response and the rate of clinical progression was observed among patients receiving a PI or NNRTI in the initial ART regimen. Nevertheless, an observational study suggests that patients receiving PI develop drug resistance less frequently following virological failure.[31] In conclusion, both NNRTI- and boosted PI-based ART have similar first-line potency, but a PI might be advantageous in particular clinical situations due to the particularly favourable resistance profile, allowing preservation of more future drug options. Similarly, no specific guidelines exist for the choice of backbone ART, i.e. nucleoside reverse transcriptase inhibitors (NRTI), in late presenters. However, tenofovir, when used in conjunction with didanosine and zidovu-dine, has tended to be associated with lower CD4 T cell

increases in recent studies.[33–35] The clinical significance of sub-optimal initial CD4 T cell increase remains unclear. Although late presentation with low baseline CD4 T cell count is the strongest prognostic factor for early mortality in both low and high income countries,[19] data from a large cohort study suggest that even patients starting ART with very low CD4 T cell counts show sustained significant immunological recovery over 5 years of ART.[36] The majority of very late presenters with severe opportunistic infections will survive due to the availability of very potent antiretroviral drugs.

In conclusion, late presentation is associated with a poorer short-term outcome as well as possibly worse long-term prognosis. Recent advances in HIV treatment make this issue more urgent. It is important to state that care and management of late presenters have shown impressive progress. Among these advances, the understanding and better management of late presentation in conjunction with opportunistic infections, the handling of side effects and drug–drug interactions, the management of severe infections such as *Pneumocystis jirovecii* pneumonia and/or tuberculosis have clearly improved survival of these patients. Nevertheless, appropriate management of late presentation with severe advanced HIV disease is critical. Prognosis depends much upon the expertise and knowledge of HIV experts, internists and, if needed, intensive care specialists. In view of the public health implications of early HIV diagnosis for reducing HIV transmission and preventing late presentation, HIV testing should be more frequently recommended in all healthcare settings. HIV screening is currently recommended for all pregnant women, and at least annually for persons at high risk of HIV infection.[37] It is to be hoped that in the future the clinical entity of late presentation will become significantly rarer.

## Transparency declarations

None to declare.

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