Immunological recovery and antiretroviral therapy in HIV-1 infection

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Potent antiretroviral therapy has dramatically improved the prognosis of patients infected with HIV-1. Primary and secondary prophylaxis against Pneumocystis carinii, Mycobacterium avium, cytomegalovirus, and other pathogens can be discontinued safely once CD4 cell counts have increased beyond pathogen-specific thresholds. Approximately one-third of individuals receiving antiretroviral therapy will not reach CD4 cell counts above 500 cells per µL after 5 years despite continuous suppression of plasma HIV-1 RNA. Whether this failure represents a risk factor for the long-term incidence of opportunistic diseases—eg, tuberculosis or malignancies—remains uncertain. We describe the time course of CD4 cell concentrations in patients whose plasma HIV-1 RNA is durably suppressed by antiretroviral therapy, in patients with incomplete suppression of plasma HIV-1 RNA, and during treatment interruptions. In addition, immune reconstitution disease, an inflammatory syndrome associated with immunological recovery occurring days to weeks after the start of antiretroviral therapy, is briefly described.

Introduction

HIV-1 infection is characterised by the continuous loss of CD4 T cells, leading to immunodeficiency, opportunistic diseases, and death. A clear inverse relation exists between the number of CD4 cells in peripheral blood and the risk of HIV-1-associated diseases. Hence, CD4 cell count in peripheral blood represents the principal surrogate marker for clinical symptoms and AIDS-defining illnesses. Persistently low CD4 cell counts below 200 cells per µL are a major criterion for initiating primary or secondary prophylaxis against opportunistic infections. The frequency of opportunistic infections dramatically declines upon initiation of antiretroviral therapy and the subsequent increase in CD4 cell count. Data from the ART collaboration, which examined 12,574 patients who had started antiretroviral therapy, showed that baseline CD4 cell count strongly predicted the probability of AIDS or death (figure 1). In particular, patients in strata below 200 CD4 cells per µL demonstrated a poor clinical outcome.

In addition, in a multivariate analysis, age, intravenous drug use, and baseline CDC stage C in the patient history predicted AIDS and death. The CD4 cell range reached by treated patients strongly depends on CD4 cell values at baseline. Hence, antiretroviral therapy needs to be initiated early enough to limit the risk of opportunistic diseases and ensure the recovery of the immune system.

After the initiation of antiretroviral therapy only a small proportion of HIV-1-infected individuals remain below 200 CD4 cells per µL. Most patients reach CD4 cell counts clearly above this critical threshold. The impact of immune recovery is best reflected by the dramatic decline of morbidity and mortality in HIV-1-infected patients since the introduction of potent antiretroviral therapy. This trend has become even more evident in recent years.

We describe the recovery of CD4 cells in different settings—eg, completely and incompletely suppressed plasma HIV-1 RNA. We also highlight the impact of different treatment strategies on CD4 cell recovery, consider the effect of scheduled treatment interruptions on CD4 cell count, and briefly describe immune reconstitution syndrome after the initiation of antiretroviral therapy.

Recovery of pathogen-specific CD4 cell function

Antiretroviral therapy results in an increase in the number of CD4 cells and the functional reconstitution of the immune system. Qualitative and quantitative recovery of pathogen-specific cellular and humoral immune responses are observed for a number of organisms including mycobacteria, cytomegalovirus, Epstein-Barr virus, hepatitis B and C virus, and Candida albicans, but not for HIV-1 itself. In observational and randomised prospective clinical studies, it has been proven safe to discontinue primary and secondary prophylaxis against a variety of pathogens—eg, Pneumocystis carinii, Mycobacterium avium complex (MAC) infections, and Cryptococcus neoformans—when CD4 cell count has reached a minimum of at least 200 cells per µL for 3–6 months (table). Secondary prophylaxis against cytomegalovirus...
was even successfully discontinued at 75 CD4 cells per μL.11 The lowest CD4 cell count before antiretroviral therapy may be important as well. In one study, the number of circulating CD4 cells before antiretroviral therapy predicted the immune response to vaccination with tetanus and diptheria toxoid, whereas the current CD4 cell count was not associated with the response to vaccination.12 It appears that a small proportion of patients are unable to completely restore CD4 cell count and particularly the repertoire of CD4 cells, which may trigger the occurrence of opportunistic infections.13 Nevertheless, it is safe to discontinue primary and secondary prophylaxis when opportunistic infections are inactive, antiretroviral therapy has been initiated, and a stable CD4 cell count above pathogen specific thresholds is present.14

**Recovery of CD4 cells after initiation of antiretroviral therapy and when plasma HIV-1 RNA is completely suppressed**

After the initiation of antiretroviral therapy, peripheral CD4 cell count starts rising, continuing for at least 3–5 years.15 The initial increase in CD4 cell count is very rapid and is usually observed in the first 3–6 months.16 This initial increase relies on a reduction in T-cell activation and primarily consists of a release of memory CD4 cells trapped in the lymphoid tissue.17 A second phase of slower increase follows, approaching stable CD4 cell counts at 4–6 years (figure 2).18 During this second phase, naive CD4 T-lymphocytes from the thymus, as well as memory CD4 T-lymphocytes, contribute to the reconstitution of the immune system. Achieving a CD4 cell count over specific thresholds (eg, 200 cells per μL) depends on baseline CD4 cell count and may take substantially longer in patients who initiate antiretroviral therapy at lower values (figure 2).19,20

The factors that determine CD4 cell responses are only partly known and depend on both the host and the virus. Considerable individual variation in the reconstitution of CD4 T-lymphocytes has been noted. In HIV-1-infected patients with excellent virological responses and continuous plasma HIV-1 RNA levels below 1000 copies per mL, higher age, a longer duration of HIV-1 infection, and lower CD4 cell count at baseline represent important risk factors for maintaining lower CD4 cell counts.21 In a recent study of the Swiss HIV Cohort, 36% of patients receiving antiretroviral therapy did not reach CD4 cell counts above 500 cells per μL after 5 years despite continuous suppression of plasma HIV-1 RNA to levels below 1000 copies per mL, and almost half of these patients reached a plateau in CD4 cell count. Hence, the number of patients with CD4 cell counts in the normal range after 4–5 years of antiretroviral therapy is smaller than expected.22 Theoretical factors that may impede a complete recovery of CD4 cells include increased viral pathogenicity or certain host factors such as insufficient thymic supply of T lymphocytes.23 In addition, virus-induced cell death and higher rates of T-cell apoptosis may occur in patients with well suppressed plasma HIV-1 RNA.24 It is much debated whether some co-infections—eg, HIV/hepatitis C virus—may limit CD4 cell recovery, whereas other co-infections—eg, HIV/GB virus C—appear to enhance increases in CD4 cell count.40–50 In general, it can be postulated that a lower CD4 cell count at initiation of antiretroviral therapy requires longer...
CD4 cell counts recover to substantially different levels, depending on long-term suppression of plasma HIV-1 RNA.

**Recovery of CD4 cells with incomplete suppression of plasma HIV-1 RNA**

Poorly suppressed HIV-1 replication is a major factor impeding the recovery of CD4 cells, leading to increased virus-related cell death and apoptosis. In patients treated successfully with antiretroviral therapy during an observation time of 4 years, CD4 cells rose to significantly higher levels compared with patients showing fewer than 75% of levels below 400 copies per mL (p<0.05; figure 3). If the viral load is not completely suppressed, viral strains with reduced fitness and pathogenicity may emerge through antiretroviral drug pressure. Deeks and colleagues demonstrated that CD4 cells remained at a similar level even when plasma HIV-1 RNA rebounded on antiretroviral therapy, suggesting reduced pathogenicity of the virus.

The failure of all three major classes of antiretroviral represents a special situation. In the Pursuing Later Treatment Options (PLATO) study the relation between plasma HIV-1 RNA, CD4 cell count, and clinical outcome was investigated in 2488 people with virological failure to all three classes of drugs, suggesting that most of these patients had highly resistant virus. A viral load of up to 10000 copies per mL was associated with stable or increasing CD4 cell counts, whereas higher plasma HIV-1 RNA values resulted in a decline in CD4 cell count. Hence, in patients with plasma HIV-1 RNA levels below 10000 copies per mL, reduced viral fitness probably compensated for the lack of suppression of HIV-1. Therefore, in the case of stable CD4 cell counts on antiretroviral therapy, it appears to be a reasonable option to wait for alternative antiretroviral drug regimens with a higher chance of complete viral suppression. However, in the situation of triple class failure when plasma HIV-1 RNA levels exceed 10000 copies per mL, the risk of death was 15-8 times higher than in patients with lower plasma HIV-1 RNA and CD4 cell counts above 200 cells per μL. This finding indicates a shift in balance and increase in pathogenicity despite the selection for drug-resistance mutations that reduce viral fitness by both nucleoside analogues and protease inhibitors. In the latter situation, a fast optimisation of antiretroviral therapy is inevitable and the time course of CD4 cells needs to be watched very closely.

Another way to expand peripheral CD4 cells in patients with incomplete viral suppression is the application of interleukin-2. In one study, intermittent cycles of interleukin-2 increased the survival of naive (CD27+CD45R0−) and memory (CD27+CD45R0+) CD4 cells. The median half-life of CD4 cells changed from 1-7 weeks to 28-7 weeks. However, the immunological function of effector memory cells against pathogens did not improve. It is therefore important to wait for the results of larger trials that analyse the impact of interleukin-2 on the reduction of opportunistic infections.

Completely suppressed plasma HIV-1 RNA is not required for an increase or stabilisation of CD4 cell count. However, incomplete suppression of plasma HIV-1 RNA may result in a larger degree of antiretroviral drug resistance over time, ultimately leading to the loss of virological control and loss of immunological recovery.

**Recovery of CD4 cells with different antiretroviral regimens**

Effective antiretroviral therapy is usually accompanied by an immunological recovery, CD4 cell increase, and decline in HIV-1 RNA. However, there are a few exceptions to this rule. Recent evaluations of patients treated with tenofovir and a didanosine dose of more than 4-1 mg/kg demonstrated a negative impact of this particular combination on the recovery of CD4 cells. The lack of increase in CD4 cell count may also be the result of other drugs such as zidovudine, particularly in combination with potentially myelotoxic drugs such as trimethoprim and sulfamethoxazole.

Unfortunately, there are only a few studies that examine CD4 cell recovery with identical antiretroviral therapies over several years. The main reason is the frequent change of the antiretroviral drug regimen during longer observation periods. In the Swiss HIV Cohort study, antiretroviral therapy initiated between January 1996 and December 1998 was changed in more than 70% of patients. Most of the investigated 1140 patients had one or two treatment changes. In half of these patients plasma HIV-1 RNA was

![Figure 3: CD4 cell recovery and different degrees of suppression of plasma HIV-1 RNA](http://infection.thelancet.com) CD4 cell counts recover to substantially different levels, depending on long-term suppression of plasma HIV-1 RNA.
well controlled and treatment changes became necessary to reduce adverse events or pill burden. Importantly, treatment changes per se and simplification does not affect increasing CD4 cell counts as long as the virological response to antiretroviral therapy remains excellent.\textsuperscript{40,41}

In general, recovery of CD4 cell counts follows very similar strata, usually being independent of the antiretroviral drug regimen. In a recent meta-analysis, protease inhibitor-containing antiretroviral therapies had a small advantage over non-nucleoside reverse transcriptase inhibitors with regard to immunological recovery.\textsuperscript{71} However, these results are difficult to interpret due to possible confounders—eg, the change of the comedication, newer antiretroviral drugs, or differences in the study population.

**Interruption of antiretroviral therapy and the impact on immunological recovery**

Toxicity, resistance, and high costs remain the major drawbacks of continuous therapy.\textsuperscript{72-75} Scheduled treatment interruptions represent one potential strategy to address these problems and are therefore extensively investigated in different clinical settings, notably in developing countries.\textsuperscript{76-78} Another goal is the maintenance or even enhancement of the response of HIV-1-specific CD8 and CD4 T cells after antiretroviral treatment interruptions.\textsuperscript{77,78} In macaques with acute simian immunodeficiency virus infection, intermittent therapy showed promising enhancements of immunological responses.\textsuperscript{79} In human studies, only a few patients experience an enhancement of HIV-1-specific immunity. In most individuals, HIV-1-specific CD8 T-lymphocytes were maintained, but not enhanced over consecutive interruptions. Therefore, it appears that the interruption of antiretroviral therapy simply restores the level of recognition of HIV-1.\textsuperscript{80,81}

**Scheduled interruption of antiretroviral therapy and immunological recovery**

Different schedules of interruption of antiretroviral therapy are under investigation. Figure 4 summarises the rationale and principle of treatment interruptions guided by CD4 cell count. Fixed cycles were viewed as particularly appealing because they followed an easy and understandable schedule without the need to tailor antiretroviral therapy to laboratory results. In one study that included 392 patients with plasma HIV-1 RNA levels below 400 copies per mL and a median CD4 cell count of 740 cells per µL, six cycles of 8 weeks on and 8 weeks off therapy were analysed.\textsuperscript{82} After 96 weeks, CD4 cell counts in the on/off group were lower than in the continuous therapy arm; however, the proportions of patients with CD4 cell counts below 300 cells per µL were not statistically different. Another small pilot study suggested that a schedule of 1 week on and 1 week off treatment would be attractive, resulting in undetectable viral loads and stable CD4 cell counts.\textsuperscript{83} However, when this concept was further tested in a larger comparative trial, 53% of patients experienced virological failure after 8 weeks.\textsuperscript{84} Similar disappointing results were recently reported from another week on/week off study with an increased development of drug resistance.\textsuperscript{85} These results are not reassuring. Both studies were terminated very early and there is little doubt that numerous interruptions of antiretroviral therapy, with frequent exposure of the virus to subinhibitory drug concentrations, would ultimately lead to an increased rate of drug resistance. Hence, even with a similar recovery of CD4 cells, this concept of fixed short cycles, in particular very short ones, has to be viewed very critically.

Attention has now shifted towards variable cycles, a strategy of intermittent antiretroviral therapy guided by CD4 cell count in which treatment interruptions are less frequent and last longer. According to this schedule, antiretroviral therapy is restarted when a patient’s CD4 cell count reaches a lower threshold at which the risk of opportunistic infections increases. In one study, the Staccato trial,\textsuperscript{86} antiretroviral therapy was restarted when patients crossed the threshold of 350 cells per µL. The virological failure rate remained low and was statistically comparable in the CD4 guided arm and the continuous treatment arm. Some drug resistance mutations were induced by interruption cycles guided by CD4 cell counts; none of these mutations were major. Treatment-related adverse events were more frequent in the continuous arm, but minor manifestations were more frequent in the scheduled interruption arm and were associated with lower CD4 cell counts. In another study, the increase in CD4 cell count was more rapid when patients were naive to antiretroviral therapy before the initiation of the study.\textsuperscript{86}

Only a few patients maintain virological control off treatment. Scheduled treatment interruptions are usually

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**Figure 4:** Effect of scheduled treatment interruptions on CD4 cell recovery in well-controlled HIV-1 infection

After treatment interruption CD4 cell count (blue line) usually declines. Scheduled treatment interruptions with CD4 guidance takes advantage of CD4 cell thresholds to discontinue (eg, >350 cells per µL) and restart antiretroviral therapy (eg, <250 CD4 per µL). This principle assumes that an HIV-1-infected individual remains at very low risk of opportunistic diseases as long as the CD4 cell count is above a critical threshold. Viral load (red line) mostly increases during antiretroviral therapy interruption. ART=antiretroviral therapy; STI=scheduled treatment interruption.
associated with a decline in CD4 cell count. Monitoring can help to maintain a safe level of CD4 cells. Restarting antiretroviral therapy in patients showing marked declines in CD4 cell count usually produces rapid increases in CD4 cell counts. However, a major negative effect may be the development of drug resistance through this strategy. Whether a lower CD4 cell count during treatment interruption is clinically safe in the long term, and at what CD4 cell threshold antiretroviral therapy should be restarted remains to be shown. The Strategies for Management of Antiretroviral Therapy (SMART) trial, which included 5472 patients and defined a threshold of 250 CD4 cells per μL for restarting antiretroviral therapy, was recently suspended because of an excess of AIDS-related opportunistic infections and deaths in the interrupted treatment group. Importantly, AIDS-unrelated deaths were also more frequently observed in the discontinuation group. Careful analysis of this trial is needed to weigh the risks of scheduled treatment interruptions and continuous therapy.

**Interruption of antiretroviral therapy as a salvage strategy**

During antiretroviral therapy, drug-sensitive quasispecies may be overgrown by resistant HIV-1 strains. Without a selective pressure, such drug-sensitive quasispecies may again replace resistant virus, suggesting that scheduled treatment interruption might improve the results of a subsequent salvage therapy. However, during “salvage” interruptions, CD4 cells often decline very rapidly, sometimes to very low values (figure 5). This decline may be without consequence at high CD4 cell levels, but when immunodefi ciency is advanced, any further decline in CD4 cell count exposes patients to an increased risk of opportunistic diseases. In a large prospective trial, the hope of an improved response to salvage antiretroviral therapy was dashed by a more rapid progression of HIV-1 infection. On the otherhand, a shorter interruption period demonstrated a benefi cial eff ect on virological response and CD4 cell increase. With the advent of new drugs and drug classes, highly resistant viruses can be targeted more effi ciently, which may further limit the value of such salvage strategies.

**Immune reconstitution disease**

Shortly after the introduction of zidovudine monotherapy, physicians noted that patients with disseminated MAC infection experienced an increase in symptoms after the initiation of antiretroviral therapy. An estimated 10–25% of patients starting antiretroviral therapy at very low CD4 cell counts—ie, below 50–100 cells per μL—may be affected by an “immune reconstitution disease” or “immune reconstitution syndrome”, thought to result from infl ammatory reactions to a previously asymptomatic pathogen. How immune reconstitution disease develops is not yet well understood, in particular whether similar mechanisms are involved in response to different pathogens. For mycobacterial infl ammatory responses may have a crucial role. Individual genetic traits—eg, major histocompatibility complex haplotypes or cytokine gene polymorphisms—may infl uence the likelihood of immune reconstitution disease. The specific immune response against microbial antigens occurring shortly after the initiation of antiretroviral therapy may either represent an adequate infl ammatory response that was previously masked by severe immunodefi ciency or an overshooting infl ammatory reaction.

The diagnostic criteria of immune reconstitution disease include a previous diagnosis of AIDS, concurrent antiretroviral therapy with increasing CD4 cell count, and an exacerbation and/or atypical presentations of opportunistic infections. Atypical presentations have been described as localised diseases, exaggerated or atypical infl ammatory reactions, and worsening of pre-existing diseases. The first symptoms of immune reconstitution disease may occur as early as a few days after the initiation of antiretroviral therapy, but most symptoms present after 2–8 weeks. Aff ected patients usually have low baseline CD4 cell counts below 50 cells per μL. Immune reconstitution disease is often associated with tuberculosis, occurring weeks after the initiation of antiretroviral therapy. This coinfection is a particular problem in developing countries where HIV/tuberculosis coinfection is frequent and immune reconstitution disease is observed in 7–40% of patients. The immunological response and severity of clinical symptoms vary, sometimes becoming life threatening. More than 20 infectious pathogens causing immune reconstitution disease have been described. For some

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**Figure 5: Effect of scheduled treatment interruption on CD4 cell recovery in salvage situations**

This principle assumes that drug-resistant virus is replaced by wild-type virus and that HIV-1 can be suppressed more effi ciently by salvage therapy. However, during a salvage situation and interruption of antiretroviral therapy, CD4 cell counts may decline to low or very low values depending on CD4 cell levels at the time of interruption. This CD4 cell count decline may be very rapid and due to a reversion of a resistant, less fi t virus to a wild-type virus associated with increased pathogenicity and increased risk of opportunistic infections. ART=antiretroviral therapy; STI=scheduled treatment interruption.
active coinfections—e.g., tuberculosis or cryptococcosis—antiretroviral therapy should be delayed during the initial phase to treat the opportunistic infection. The results of the AIDS Clinical Trials Group study (ACTG 5164), which is prospectively evaluating patients receiving antiretroviral therapy within 2 weeks of starting therapy for acute opportunistic infections versus patients who will have antiretroviral therapy deferred at least for 4 weeks, are eagerly awaited.

However, in general, since immune recovery is very important with regard to HIV-1 prognosis, particularly in the first 6 months, antiretroviral therapy is continued despite immune reconstitution disease. If life-threatening events occur or steroids are ineffective, one should consider pausing antiretroviral therapy.

Conclusion
Antiretroviral therapy usually results in a biphasic increase in CD4 cell count. More than 95% of successfully treated individuals with well-controlled HIV-1 viremia reach a CD4 cell count of more than 200 cells per μL. However, one-third of successfully treated patients appear not to reach a normal CD4 cell count within 5 years. This observation raises concerns for the long-term prognosis of these patients and suggests that antiretroviral therapy should be initiated before CD4 cell counts fall below a certain threshold. With adequate monitoring, CD4 cell counts can be maintained above prespecified levels during scheduled treatment interruptions. However, a lower CD4 cell count may expose patients to an increased risk of clinical events. This risk needs to be carefully balanced against the potential benefits associated with decreased exposure to antiretroviral drugs.

Conflicts of interest
MB has acted as an investigator for Abbott, Boehringer-Ingelheim, GlaxoSmithKline (GSK), and Hoffmann-LaRoche-Trimeris; and has received research grants from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, GSK, Hoffmann-LaRoche-Trimeris, Merck Sharp and Dohme-Chibret. He has received speaker honoraria from Abbott, GSK, and Hoffmann-LaRoche-Trimeris. In addition, MB has been involved in the treatment of patients with advanced HIV infection and has worked with patients infected with HIV-1.

References


