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Early Versus Delayed Antiretroviral Therapy in Patients with HIV Infection

A Review of the Current Guidelines from an Immunological Perspective

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Abstract

The development and implementation of highly active antiretroviral therapy (HAART) for the treatment of the human immunodeficiency virus has revolutionised the care of patients with this disease. Despite the positive impact that antiretroviral therapy has had on the lives of individuals with HIV infection, the adverse effects, potential long-term toxicities, complexity of regimens, development of drug resistance and cost have made decisions about when to initiate HAART difficult. The benefits and risks of antiretroviral therapy vary considerably among patients at different stages of disease, mainly as a result of the irreversible destruction of the immune system that occurs as HIV infection progresses.

In acute HIV infection, the primary aim of treatment is preservation and reconstitution of HIV-specific immune function. In symptomatic or late-stage disease, the goal is control of viral replication with resulting improvement in non-HIV-specific immunity, which leads to decreased morbidity and increased survival. The most controversial decision involves when to start therapy in persons with asymptomatic chronic HIV, where the benefits are less well established and may be outweighed by the drawbacks, depending on the individual patient.

In all patients, the advantages and disadvantages must be considered carefully, and the readiness and ability of the individual to adhere to a complex multidrug regimen needs to be assessed before the initiation of therapy.

Since the early 1980s, when HIV was first recognised, it has become a leading threat to health worldwide. Despite aggressive research initiatives and unprecedented speed in the development of antiretroviral medications, the Joint United Nations Programme on HIV/AIDS estimate that 3 million people died from AIDS in 2001, while 40 million people worldwide are currently living with HIV

infection.[1] A disproportionately large percentage of these individuals live in sub-Saharan Africa, where access to proper treatment is limited. Even in the developed world, antiretroviral therapy is far from ideal, making the decision of when to initiate therapy a difficult one.

Over the past several years, the development of highly active antiretroviral therapy (HAART) has dramatically reduced the morbidity and mortality associated with HIV infection.[2-5] HAART is the use of a combination of antiretroviral drugs, most commonly including two nucleoside reverse transcriptase inhibitors (NRTI) and one protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI). Another accepted first regimen is three NRTIs, especially one that includes abacavir. The goal of this therapy is to cause an effective and durable suppression of HIV replication and limitation of infection and loss of CD4+ T helper (Th) cells, resulting in improvement in overall immune function.

Despite these benefits, combination therapy poses many problems to patients, including numerous adverse effects, long-term metabolic toxicities, development of drug resistance, diminution of quality of life, and the unknown risks of lifelong use. The lack of availability of HIV medications because of the extremely high cost of therapy and necessary healthcare, especially to patients in the developing world, make HAART even more problematic. Soon after the first use of multidrug regimens, there was much optimism about the possibility of HIV eradication, which was fuelled by the dramatic drop in plasma HIV-1 RNA to undetectable levels in many patients, as well as a striking decrease in progression to AIDS and death.[5-8] However, with the discovery of latently infected T cells in viral reservoirs it is estimated that it will take 60 years or more on HAART to achieve viral eradication and experts now conclude that curing HIV with drugs is highly unlikely.[9-12] A recent study suggests that viral escape mutations occur that prevent recognition of HIV-infected cells by CD8+ cytotoxic T cells, a critical defence against HIV; this form of viral escape can be passed vertically from mother to infant, further decreasing the likelihood of eradication.[13] Additionally, increasing evidence suggests that despite good immunological control of HIV infection, superinfection with a second strain of HIV can result in loss of antiviral control.[14,15] All of these factors affect the difficult decision of when to start HAART.

The timing of initiation of HAART is based on the primary objective of therapy. Individuals diagnosed and treated with potent antiretroviral therapy during acute HIV infection, or soon after seroconversion, are able to retain HIV-specific CD4+ Th cell function.[16] In this situation, the goal of therapy is preservation of virus-specific immune responses presumed to be central for immunity against HIV itself. In persons with chronic HIV infection, the objective of therapy shifts away from trying to preserve or restore HIV-specific immunity and towards improvement in non-specific immune function to slow the progression of disease. In individuals with clinically advanced infection, initiation of therapy is also aimed at delaying progression of disease, and improving morbidity and mortality by limiting the development of AIDS-associated opportunistic infections. The differences in objectives of therapy and immunological impact of HAART in patients at different stages of disease have helped to guide expert panels in making recommendations of when to initiate treatment. Many issues remain controversial, including that of the timing of initiation of therapy in patients with asymptomatic disease, and differences in levels of viraemia between men and women with HIV. In this manuscript, we review the existing recommendations for when to initiate antiretroviral therapy as well as pointing out the controversies that remain.

1. Current Recommendations

Recommendations for when to initiate HAART have changed significantly over the past few years, and differ among the various advisory panels (table I). The major panels include the Department of Health and Human Services and the Henry J. Kaiser Family Foundation (DHHS in the US), the Interna-

Table I. Recommendations for when to initiate highly active antiretroviral therapy

Infection	CD4+ T-cell count (cells/μL)	Plasma HIV RNA (copies/mL)	BHIVA[19]	IAS[18]	DHHS[17]
Acute	Any	Any	Consider treatment; enrol in clinical trial		Consider treatment
Symptomatic	Any	Any	Treat	Treat	Treat
Asymptomatic	<200	Any	Treat	Treat	Treat
Asymptomatic	>200			Treatment individualised[a]	
Asymptomatic	200–350	Any	Consider treatment		Treatment generally offered, although controversial
Asymptomatic	>350	Any	Defer		
Asymptomatic	>350	>55 000 (RT-PCR or bDNA 3.0)			Some would treat, others would not
Asymptomatic	>350	<55 000 (RT-PCR or bDNA 3.0)			Certain clinicians would defer treatment

a Based on CD4+ cell count and rate of decline HIV RNA (>50–100K is high), patient interest and adherence, toxicity and drug-drug interactions.

bDNA = branched-chain DNA; **BHIVA** = British HIV Association; **DHHS** = Department of Health and Human Services; **IAS** = International AIDS Society; **RT-PCR** = reverse transcriptase polymerase chain reaction.

tional AIDS Society – USA panel (IAS), and the British HIV Association (BHIVA).[17-19]

There is consensus among the three groups that all patients with symptomatic HIV-1 infection should be treated with HAART. There is also agreement that any patient with a CD4+ T-cell count <200 cells/μL (normal range 350–1500 cells/μL; varies depending on laboratory) should be treated, regardless of plasma HIV-1 RNA viral load.

For all other clinical scenarios, there are differing recommendations among the groups, not surprisingly, given the lack of data clearly supporting a given treatment strategy. In the past, more weight was placed on the viral load, whereas now all three groups focus primarily on the CD4+ T-cell count to dictate timing of initiation of HAART. When the CD4+ T-cell count is between 200–350 cells/μL, the BHIVA recommends consideration of therapy, depending on the rate of CD4+ T-cell count decline, viral load, symptoms and the patient's wishes. The IAS also recommends an individualised approach to treatment in patients with a CD4+ T-cell count >200 cells/μL, with the decision hinging on the above-mentioned immunological and virological parameters, patient interest and adherence, toxicity and drug-drug interactions. The DHHS suggests the most aggressive approach, as they generally recommend treatment in patients with a CD4+ T-cell count between 200–350 cells/μL, although they acknowledge that this remains controversial.

None of the groups advocate treatment for all patients with acute HIV infection, although the BHIVA recommends consideration of treatment, especially through enrolment in a clinical trial. The DHHS recommends consideration of treatment in patients with acute HIV-1 infection. The IAS does not address this issue in their recently published recommendations. This discussion will try to clarify the issues, using data on the immune responses generated in individuals treated with HAART during acute HIV-1 infection, chronic asymptomatic infection, and chronic symptomatic or advanced disease.

2. Considerations Regarding the Use of HAART

After the widespread introduction of highly active antiretroviral agents, there was much optimism about the possibility of eradicating HIV in infected patients.[7,20] Soon thereafter, it became clear that this is extremely unlikely. The primary reason for this is the presence of viral reservoirs, privileged

Table II. Pros and cons of early versus delayed highly active antiretroviral therapy

Treatment	Acute	Chronic	References
Early			
Pros			
Preservation of HIV-specific immune function	+++	±	14,21,22
Preservation of non HIV-specific immune function	+++	++	23-26
Decreased viral load set-point	++		27,28
Slowing of progression to AIDS	+	++	5,29
OI prophylaxis may be unnecessary	NA	++	30-34
Decreased viral transmission	++	++	35
Limitation of viral diversity	++	+	21
Limitation of viral reservoirs	++	+	36
Cons			
Toxicity	++	+	37
Complicated regimen to adhere to	++	++	
High cost	++	++	38 [a]
Long-term effects unknown	+	+	
Minor lapses in adherence lead to resistance	++	++	39
Fewer drugs available for future use	++	+	
Delayed			
Pros			
Avoidance of drug toxicity	+	+	37
Simplicity of not needing to adhere to a regimen	+	+	
Delay development of drug resistance mutations	+	+	
Full armamentarium of drugs available for future use	+	+	
Lack of direct drug costs	+	+	
Cons			
Irreversible loss of HIV-specific immune function	+	+	14,21,22
Increased viral transmission	++	++	35
OI prophylaxis may be necessary		+	
Increase in OIs		+	2
Faster progression to AIDS	+	+	5
Increased mortality		+	2-5
Increase in hospital admissions		+	38

a The cost to the patient at Brigham and Women's Hospital (BWH) outpatient pharmacy, Boston, MA, US, averaged, at wholesale price, $US1217 per month. Personal communication with BWH pharmacy, 2002 Feb 20.

NA = not applicable; **OI** = opportunistic infections; **+** indicates some data; **++** indicates moderate data; **+++** indicates strong data; ± indicates conflicting data.

compartments that harbour infected cells, as well as latent CD4+ T cells that remain unaffected by HAART.[10-12] Antiretroviral drugs block viral replication, but have no activity against nonreplicating virus harboured by quiescent cells. The advantages and disadvantages of treatment must be seriously evaluated in all patients with HIV, in light of the current goal of HAART, which is control of HIV and preservation of CD4+ T cells, rather than eradication of infection (table II).

While many highly potent drugs have been developed and are commonly used, a broad array of adverse effects and toxicities has been observed. Some are life-threatening, such as the hypersensitivity reaction associated with abacavir;[40] Stevens-Johnson syndrome and drug rash with eosinophilia and systemic symptoms (DRESS) associated with

nevirapine;[41-43] fatal hepatitis associated with nevirapine;[44,45] and lactic acidosis with hepatic steatosis associated with NRTIs, especially stavudine (d4T) with or without didanosine (ddI).[46-51] Three fatal cases of lactic acidosis with or without pancreatitis have occurred in pregnant women taking stavudine with didanosine.[52] Other antiretrovirals cause metabolic effects, including dyslipidaemia, increased insulin resistance and diabetes mellitus, osteopenia, osteoporosis and the lipodystrophy syndrome.[53-61] Given the frequency and known consequences of these problems, it is expected that they will contribute to overall morbidity, although the long-term effects for this group of patients remain unclear. There have already been documented cases of premature coronary artery disease in patients taking PIs.[62,63] Other dangerous toxicities include bleeding associated with PIs especially in, but not limited to, individuals with haemophilia; pancreatitis associated with didanosine and PIs; and granulocytopenia and severe anaemia associated with zidovudine.[64-67] There are also numerous unpleasant adverse effects, such as headaches, mouth ulcers, nausea, diarrhoea and peripheral neuropathy, among others.[37] There are many potential drug-drug interactions, some of which are probably not yet known, since antiretroviral drugs are relatively new and unique combinations are continually being tried.

Many additional factors need to be taken into account when considering HAART. The most common regimens include three drugs, requiring multiple doses each day, as well as various dietary rules. Adherence to these complicated regimens is difficult, and even a slight lapse in proper dosage can lead to the development of drug resistance mutations and loss of durable viral suppression.[39] Another potential drawback to treatment is the immune reconstitution syndrome that occurs in some patients during the period of immunological recovery.[68] This is more commonly seen in patients with very low CD4+ T-cell counts before starting treatment, so that the benefit of treatment outweighs the risk of this type of reaction. Antimicrobial agents for primary or secondary prophylaxis against pathogens such as *Pneumocystis carinii* and *Mycobacterium avium* complex can be safely stopped in many patients with good immunological responses to HAART, thereby decreasing the patient's exposure to these potentially toxic medications.[30-34,69,70] Other issues include the problem of lack of availability of antiretroviral drugs, especially in the developing world. In the developed world, the cost of HAART regimens remains high, with a typical regimen of zidovudine, lamivudine and indinavir costing $US1217 per month; these figures do not take into account expenses required for the monitoring of patients while on therapy[1]. This is compounded by the necessity for lifelong use in the majority of patients.

In addition to the immunological benefits of treatment for the individual patient, there are public health ramifications of the timing of treatment. It has been demonstrated that viral load is an accurate predictor of the risk of heterosexual transmission of HIV, and that transmission is rare in persons with levels below 1500 RNA copies/mL plasma, measured by the reverse transcriptase polymerase chain reaction (RT-PCR).[35] Transmission of highly resistant virus has been observed, indicating that failure of therapy to fully suppress virus is a threat not just for the source patient but also for those infected by that individual.[71-73] These factors argue for aggressive treatment and full viral suppression in order to prevent transmission of resistant virus. However, insufficient treatment may result in the development of drug resistance which may be more detrimental than delaying treatment altogether. Therefore, the readiness of the patient to commit and fully adhere to the regimen is crucial.

3. Acute HIV-1 Infection

The DHHS recommends consideration of treatment for patients with acute or primary HIV-1 infection, which is defined as a transient symptomatic illness characterised by a high level of HIV-1 viral

1 The cost to the patient at Brigham and Women's Hospital (BWH) outpatient pharmacy, Boston, MA, US, averaged, at wholesale price, $US1217 per month. Personal communication with BWH pharmacy, 2002 Feb 20.

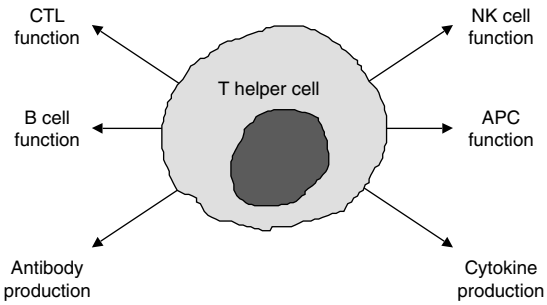

Fig. 1. CD4+ T helper cells are the central orchestrators of the immune system, signalling other cells to action through the release of cytokines. HIV-specific T helper cells are weak or absent in all stages of disease. **APC** = antigen-presenting cell; **CTL** = cytotoxic T lymphocyte; **NK** = natural killer.

replication and a negative enzyme-linked immunosorbent assay (ELISA).[74] The BHIVA recommends enrolment in a clinical trial, as data supporting treatment in this group of patients are limited; however, if enrolment in a trial is not possible, both prompt treatment and no treatment are considered reasonable. The IAS does not comment on acute HIV-1 infection in their guidelines.

The rationale for treating patients during acute infection is to try to preserve both HIV- and non-HIV-specific immunity, while possibly lowering the viral load 'set-point', which is an important prognostic marker of disease progression.[27,28] Other benefits include decreased viral diversity by suppression of viral replication and mutation, and limitation of viral reservoirs.[21,36] Additionally, there are potentially significant public health benefits of decreasing infectiousness at a time when viral replication is extremely high.[75]

The most significant and well-substantiated benefit of treating patients with acute HIV-1 infection, is that HIV-specific CD4+ T-cell responses can be preserved[16,22,76,77] which does not appear to be possible in chronic infection.[16,21] HIV-specific CD4+ T-cell proliferative responses are lost early in HIV infection, when patients remain untreated.[78] CD4+ HIV-specific T-cell responses (and to a more limited degree, CD8+ T-cell responses) can be preserved in patients treated early during acute infection.[22,76] It is hypothesised that through reduction in the amount of circulating virus with antiretroviral therapy, limitation of CD4+ T-cell activation may result in decreased infection by HIV, thereby preserving these cells which may be essential for fighting HIV (figure 1). CD4+ T-cell function is crucial for maintaining the CD8+ cytotoxic T lymphocyte (CTL) response, which in turn is necessary for control of viraemia in primary HIV-1 infection. In the absence of CD4+ T-cell help, CTLs wane in HIV infection.[16,79-83] By releasing interferon-γ and other cytokines and chemokines, CD4+ T cells provide 'help' to CD8+ T cells by stimulating killing of HIV-infected cells (figure 2).

In patients who receive therapy during this crucial early period, it may be possible to later discontinue therapy in the setting of supervised treatment interruption (STI).[77,84,85] This strategy boosts the patient's cellular immune response to HIV, through limited and controlled re-exposure to autologous virus. One recent study also showed that in patients with acute HIV undergoing STI, a subset of patients had the emergence of neutralising antibodies, which correlated with spontaneous control of rebound viraemia. This response did not occur in all patients who were able to control virus spontaneously, although it probably contributes to control in some patients.[86] This study raises the concern that pro-

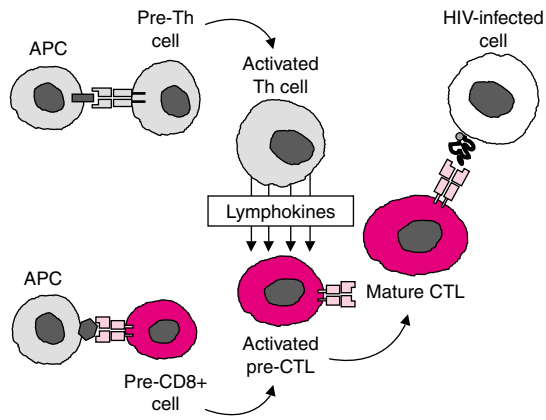

Fig. 2. HIV-1 infection, CD4+ Th cells are important for inducing a CD8+ cytotoxic T-lymphocyte (CTL) response. When HIV-1 viral particles are presented by major histocompatibility complex class II molecules on the surface of antigen presenting cells, they are recognised by CD4+ cells, which are activated and proliferate, and release antiviral cytokines, which stimulate CTLs to kill HIV-1-infected cells. **APC** = antigen-presenting cell; **Th** = T helper.

gressive destruction of HIV-specific immunity may occur during any period of viraemia, even during STI. In addition to preserving specific anti-HIV immunity, treatment during acute infection also enhances non-HIV antigen-specific immune function.[76]

From the data that have been collected on patients with acute HIV-1 infection, it is clear that prompt initiation of HAART during primary infection can preserve HIV-specific immunity, although it remains unclear whether these effects will be maintained over time.[16,22,76] These immune responses are typically weak or absent in chronically infected individuals and are not readily restored despite extended use of effective antiretroviral therapy.[21] Although the exact timing of the loss of these responses is unknown, it is possible that they begin to be depleted within the first few weeks of infection. Additionally, investigators have shown that HIV preferentially infects HIV-specific memory CD4+ T cells at all stages of disease, including during viral rebound in the setting of STI.[87] Certain experts would recommend treating patients before seroconversion and within 6 months of seroconversion, as there may still be some preservation of HIV-specific immunity possible during this brief window of time. Given the rapid and progressive destruction of the immune system following HIV infection, it is preferable to treat patients as soon as possible following the diagnosis of acute HIV infection and, therefore, healthcare providers should have a high level of suspicion when evaluating a patient with possible acute HIV infection. The case for treating patients during acute HIV will be made stronger if STI in this setting is successful for large numbers of patients over time, as this will potentially abrogate the need for long-term exposure to HAART.

4. Chronic Asymptomatic HIV-1 Infection

The decision of when to start HAART during the asymptomatic phase of HIV infection remains a controversial issue, as there are few data to support the benefit of HAART before advanced destruction of the immune system. It is clear that patients with a CD4+ T-cell count <200 cells/μL will benefit from HAART, as their risk of succumbing to an opportunistic infection is high.[5,8,88-90] Many experts agree that it is unnecessary to treat asymptomatic patients with a CD4+ T-cell count >350 cells/μL, unless a precipitous decline in CD4+ T-cell count occurs. The Multicenter AIDS Cohort Study (MACS) showed that the 3-year progression to AIDS was 38.5% in patients with CD4+ T-cell counts between 201–350 cells/μL, compared with 14.3% in patients with CD4+ T-cell counts >350 cells/μL. In patients with CD4+ T-cell counts between 201–350 cells/μL, the 3-year risk of progression to AIDS was 4.1% in those with an HIV-1 RNA level <20 000 copies/mL; 36.4% in those with an HIV-1 RNA level between 20 001–55 000 copies/mL; and 64.4% in those with an HIV-1 RNA level >55 000 copies/mL.[28]

While the MACS data have been helpful in risk stratifying patients, especially at the extremes of disease, in patients with CD4+ T-cell counts between 200–350 cells/μL, the decision of when to start HAART remains difficult. A recent meta-analysis showed that the baseline CD4+ T-cell count is the dominant prognostic factor in patients starting HAART. On the basis of CD4+ T-cell count, the adjusted hazard ratios for progression to AIDS or death were 0.74 for 50–99 cells/μL, 0.52 for 100–199 cells/μL, 0.24 for 200–349 cells/μL and 0.18 for >350 cells/μL. Baseline viral load was associated with progression to AIDS or death only when >100 000 copies/mL.[90] This study showed only a 1.3% benefit to starting therapy when the CD4+ T-cell count is between 200–349 cells/μL compared with when it is ≥350 cells/μL, which was not considered significant. Recently published data from the Swiss HIV Cohort Study show that treated asymptomatic patients with a CD4+ T-cell count ≥350 cells/μL had a 4 to 5-fold decrease in risk of progression to AIDS or death compared with matched controls in whom treatment was withheld for at least 12 months. However, there was a high rate of adverse effects causing a change in at least one agent (35%), therapy interruption (41%) or complete discontinuation of HAART (24%).[29]

Generally, patients with chronic HIV infection have significant improvement in non HIV-specific immune function, but only minor restoration of HIV-specific immunity after starting HAART.[16,26] Virological and immunological responses, including suppression of viraemia, increase in CD4+ T-cell count and proliferative responses, are similar in patients with CD4+ T-cell counts above and below 500 cell/μL, which supports delaying treatment until the risk of disease progression is significant.[91] The rationale for this approach is that it will minimise long-term toxicities while protecting the advantages gained from HAART. Recently, there has been a study showing that treated patients with CD4+ T-cell counts >350 cells/μL or HIV-1 RNA viral load <25 000 have more favourable and durable responses than those with lower CD4+ T-cell counts or higher viral loads, although another study shows that lower CD4+ T-cell counts at baseline is not associated with worse virological outcome.[92,93] Several studies reveal that suppression of viral replication is easier to achieve and maintain in patients with lower baseline HIV-1 RNA levels and higher baseline CD4+ T-cell counts, although one study shows that the longer time to suppression in patients with higher baseline viral loads does not lead to any decrease in the ability to suppress virus.[92,94-97]

There is evidence showing that successfully treated patients with chronic HIV have an improvement in their CD4+ T-cell receptor repertoire.[98] A 96-week study that followed treated patients with chronic HIV who had baseline CD4+ T-cell counts of 100–500 cells/μL showed that around half of the patients developed lymphoproliferative responses to HIV p24 antigen, although these were weaker than those seen in patients with treated acute HIV infection.[99] This is in contrast to earlier data showing a lack of HIV-specific T-cell proliferation in treated patients with chronic HIV.[16,26] To date, all studies of STI in patients with chronic HIV have been disappointing, arguing that the minimal HIV-specific immune restoration that has been observed is insufficient for autonomous control of disease.[100-102] Taken together, these studies do not clearly indicate that earlier treatment of chronically infected individuals is beneficial and further research is needed to clarify this issue.

5. Symptomatic HIV-1 Infection and Advanced AIDS

All of the major advisory committees recommend treatment with HAART for patients with symptomatic HIV, defined as wasting, thrush or unexplained fever for >2 weeks, or late-stage AIDS. There is clearly a decrease in morbidity and mortality when these groups are treated. National surveillance data on 1255 patients with CD4+ T-cell counts <100 cells/μL revealed that the incidence of the three major opportunistic infections (*P. carinii* pneumonia, *M. avium* complex and cytomegalovirus [CMV]) decreased from 21.9/100 person-years in 1994 to 3.7/100 person-years by mid-1997. In the same group, mortality declined from 29.4/100 person-years in 1995 to 8.8/100 person-years in the second quarter of 1997.[2] Other studies have shown similar results, and have also proven that a three drug combination is superior to two drugs in slowing progression to AIDS and death.[103]

Although HIV-specific immunity does not recover in patients with chronic HIV receiving HAART, there is a substantial improvement in non-HIV specific immunity, which has led to a dramatic decrease in opportunistic infections, and progression to AIDS and death. In 1997, it was shown that a three drug regimen that includes a PI, is superior to PI monotherapy and to zidovudine with lamivudine in effecting a greater decline in plasma HIV-1 RNA levels and a greater increase in CD4+ T-cell count.[8] Other studies have also shown a greater viral load reduction and CD4+ T-cell count increase, as well as increased CD4+ T-cell proliferative responses against non-HIV antigens, such as CMV, tuberculosis and phytohemagglutinin.[24] The benefits to treating this group of patients are clear and every effort should be made to provide treatment for patients who are able to adhere to a HAART regimen.

6. Women and HIV

Current recommendations regarding initiation of HAART use the same virological and immunologi-

cal thresholds for both men and women, despite potential differences in HIV-1 RNA levels in early disease that have been observed in some studies, including in two recently published comprehensive meta-analyses of the available data.[104-107] Whereas level of plasma viraemia is highly predictive of disease progression in men, the same levels may not be appropriate to use for women.

Some studies have shown that women tend to have much lower plasma levels of HIV-1 RNA early in the disease, although the disease progresses just as rapidly as in men.[93,104,105,108] Viraemia in women has been found to be 0.13–0.78 log lower than that in men, with the most striking difference being at the time of seroconversion and this difference then diminishes over time.[104,106-110] Since it is often impossible to know how long a patient has been infected with HIV, clinicians should be cautious in their interpretation of the viral load of a woman as a prognostic marker. Women with the same HIV-1 RNA level as men have a 1.6-fold higher risk of AIDS; or, women with half the HIV-1 RNA level of men have a similar time to AIDS as men.[104] HIV-1 plasma RNA levels have very different kinetics in women than in men; while these levels are predictive of disease progression throughout the course of infection in men, they are only predictive in women 2 years after seroconversion.[111] Although the viral load may be lower in women than men early in disease, these values converge later in infection.[111,112] In a study comparing virological and immunological parameters in female and male injection drug users over 10 years, median initial HIV-1 RNA viral loads were 50 766 copies/mL in men but only 15 103 copies/mL in women. The median initial HIV-1 RNA viral load in men in whom AIDS developed was 77 822 copies/mL versus 40 634 copies/mL in men in whom it did not; the corresponding values in women were 17 149 and 12 043 copies/mL, respectively.

There are no clear prospective data to make similar predictions of disease progression based on viral load in women as there are for men, but it is clear that the levels used for men cannot be extrapolated to women. Gathering these data will be especially useful for helping to guide treatment in women with CD4+ T-cell counts between 200–350 cells/μL, as viral load carries greater weight in the decision of whether or not to start HAART in this CD4+ T-cell count range. Further prospective trials of disease progression in women should be conducted in order to generate useful guidelines.

7. Conclusion

In the last two decades, HIV infection has become a worldwide epidemic that is a major threat to productive age groups in the developing world, particularly in sub-Saharan Africa. This will leave large numbers of orphans, and nations without an available work force, causing unprecedented social and economic instability.[1] While the search for an effective vaccine and immunotherapy continues, HAART remains the only effective treatment for HIV. Never before has such rapid and sophisticated drug development occurred, although the results have not been without a large cost, both financially and medically; the complicated regimens have a long list of potential adverse effects, some of which are not yet known. Since the implementation of HAART, profound immunological and virological improvement has been observed, and the morbidity and mortality from HIV and AIDS has dropped dramatically.

Presently, the goal of HAART is effective and durable suppression of HIV-1 viral replication, with resulting improvement of overall immune function. In patients treated during acute HIV infection, preservation of HIV-specific immune function is also possible, which may abrogate the need for lifetime use of HAART, as some of these patients have significantly decreased viral load set-points and are able to control virus spontaneously following sustained and effective treatment with HAART. The question of when to initiate HAART in individuals with chronic HIV infection remains in flux as we gain greater insight into the immunological and virological benefits of therapy compared with the cost, adverse effects and long-term toxicities of these drugs. Currently, the guidelines are the same for women and men, although further studies need to

be conducted to clarify whether there should be different guidelines for women, given the differences in HIV-1 RNA levels during the first 2 years of infection.

A greater understanding of the immunological and virological effects of HAART, especially in patients with chronic infection and a CD4+ T-cell count between 200–350 cells/μL, may also help to clarify the optimal timing of HAART.

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