Antiretroviral therapy and management of HIV infection
Paul A Volberding, Steven G Deeks

Antiretroviral therapy of HIV infection has changed a uniformly fatal into a potentially chronic disease. There are now 17 drugs in common use for HIV treatment. Patients who can access and adhere to combination therapy should be able to achieve durable, potentially lifelong suppression of HIV replication. Despite the unquestioned success of antiretroviral therapy, limitations persist. Treatment success needs strict lifelong drug adherence. Although the widely used drugs are generally well tolerated, most have some short-term toxic effects and all have the potential for both known and unknown long-term toxic effects. Drug and administration costs limit treatment in resource-poor regions, and are a growing concern even in resource rich settings. Finally, complete or near complete control of viral replication does not fully restore health. Long-term treated patients who are on an otherwise effective regimen often show persistent immune dysfunction and have higher than expected risk for various non-AIDS-related complications, including heart, bone, liver, kidney, and neurocognitive diseases.

Introduction
Advances in understanding of HIV biology and pathogenesis, and in application of that knowledge to reduce morbidity and mortality, rank among the most impressive accomplishments in medical history. No example since penicillin rivals the development of antiretroviral drugs in controlling a previously fatal infection. Antiretroviral therapy nowadays is potent, convenient, and typically well tolerated. Treatment initiated before advanced disease stage reduces plasma HIV RNA concentrations to undetectable values in most motivated patients who have access to these drugs. Although the degree of immunological recovery varies in treated people, most who begin therapy before the onset of advanced immunodeficiency—eg, a CD4 T-cell count lower than 200 cells per μL—show robust and sustained CD4 T-cell gains. Despite the unquestioned success of modern treatment, many challenges remain. For reasons still being investigated, antiretroviral therapy does not fully restore health. HIV-infected people on such treatment have a shorter life expectancy than their do uninfected peers. This short life expectancy is especially true for patients who initiate therapy during advanced stages of their disease, but might even be true for optimally treated patients. Many patients continue to have long-term toxic effects from drugs that were once widely used in resource-rich parts of the world, and these effects are a growing concern even in resource rich settings. Finally, complete or near complete control of viral replication does not fully restore health. Long-term treated patients who are on an otherwise effective regimen often show persistent immune dysfunction and have higher than expected risk for various non-AIDS-related complications, including heart, bone, liver, kidney, and neurocognitive diseases.

Search strategy and selection criteria
PubMed was searched with the broad terms of “HIV and antiretroviral therapy” with filters of research articles, clinical trials, reviews, meta-analyses in adults, and the English language to identify a large collection of potential articles for this Seminar. Papers deemed most relevant to this Seminar were selected, focusing on those as recent as possible, apart from important early work. Emphasis was placed on larger trials and cohorts and longer periods of treatment or observation. An attempt was made to select references from all affected regions of the world.
deficiency, later termed acquired immune deficiency syndrome (AIDS), was reported in 1981. Even the earliest reports of AIDS noted a striking depletion of CD4 T lymphocytes and expansion of activated CD8 T cells. HIV was first cultured in 1983 and rapidly established as the causative agent of AIDS. Diagnostic tests for circulating HIV antibodies further clarified the epidemiology and transmission of the virus and identified the enormous scale of the epidemic, with over 1 million people testing positive by 1995 in the USA alone.

An initial and expanding investment of US$1 billion in new grants from the US National Institutes of Health recommended by a panel of the Institute of Medicine of the US National Academy of Sciences in 1986 fuelled an unprecedented pace of discovery of the basic biology of HIV infection. Other nations also rapidly joined a large international effort to address the epidemiology, pathogenesis, and treatment of this disease. Studies during this period led to a detailed understanding of every step in the viral life cycle (figure 1). Many of these steps were later used by the pharmaceutical industry for drug development. As a result of this partnership, 23 drugs have been approved, with most still being generally used in clinical practice (table).

**Natural history of untreated HIV infection**

HIV infection follows sexual or parenteral exposure to HIV-containing fluids. In vaginal exposure, HIV attaches to target cells that carry it to regional lymph nodes in which it replicates and quickly establishes a productive and permanent infection. Once infection is systemic, HIV preferentially targets CCR5 CD4 memory T lymphocytes in the gastrointestinal tract, a crucial element in host defence in the gut. By contrast with peripheral blood CD4 cell counts, which decline slowly in most patients, the gut CD4 population is rapidly, massively, and perhaps permanently depleted. All body compartments, including the CNS, become infected in the early phase of the disease.

Initial HIV infection is often symptomatic. Many experience an acute retroviral syndrome characterised by fevers, malaise, generalised lymphadenopathy, pharyngitis, diarrhoea, and rash. Possible abnormalities in laboratory tests include liver function disturbances and pancytopenia. Since this symptom complex is not specific, acute infection is often unrealised. In primary infection, plasma HIV RNA concentrations can be very high, making secondary transmission a high risk if the newly infected person continues to engage in unprotected sexual activity or needle sharing. Since as much as 40–50% of all transmission events in men who have sex with men are thought to occur in the context of acute infection (the frequency in heterosexual partners is not known), identification, treatment, and counselling of affected individuals is a key public health focus.

After the symptoms of primary HIV infection resolve, the infected person enters a phase of asymptomatic disease. This stage can persist for several years, although rapid progression is fairly common. Symptomatic disease often emerges as the peripheral CD4 cell count falls to lower than 350 cells per µL. The risk of classic AIDS-defining events becomes more apparent at even lower T-cell counts, with many occurring at less than 200 cells per µL (eg, Pneumocystis jirovecii pneumonia, Kaposi’s sarcoma) or less than 50 cells per µL (eg, cytomegalovirus retinitis, CNS non-Hodgkin’s lymphoma). Despite this classic and often predictable natural history, emphasis should be put on the fact that some serious complications such as bacterial pneumonia, Kaposi’s sarcoma, non-Hodgkin’s lymphoma, and tuberculosis can occur in patients with high CD4 T-cell counts.

Although most untreated patients will eventually die from the disease, a few naturally control their HIV infection. These so-called elite controllers are the focus of intense investigation for insights into two of the most important challenges facing the specialty: the development of an effective vaccine and a functional cure.

---

**Figure 1: HIV life cycle and antiretroviral drug targets**

Present antiretroviral drugs span six classes that target five unique steps in the HIV life cycle (binding, fusion, reverse transcription, integration, and proteolytic cleavage). The most common drugs used in resource-rich regions to target each step are shown. Extracellular virions enter their target cell through a complex three-step process, which is (1) attachment to the CD4 receptor, (2) binding to the CCR5 or CXCR4 coreceptors, or both, and (3) membrane fusion. Maraviroc blocks CCR5 binding and enfuvirtide blocks fusion. The HIV reverse transcriptase enzyme catalyses transcription of HIV RNA into double-stranded HIV DNA, a step inhibited by nucleoside analogues and non-nucleoside reverse transcriptase inhibitors (NNRTIs). The HIV integrase enzyme facilitates incorporation of HIV DNA into host chromosomes and this step is inhibited by raltegravir and other integrase inhibitors. After transcription and translation of the HIV genome, immature virions are produced and bud from the cell surface. The HIV protease enzyme cleaves polypeptide chains, allowing the virus to mature. This last step is inhibited by HIV protease inhibitors.
Despite 30 years of continued investigation, the precise mechanism of CD4 T-cell loss induced by HIV infection remains controversial. HIV-mediated destruction of its preferred target, the activated CD4 T cell, is certainly central to HIV pathogenesis, but does not explain why many uninfected cells die or why the host cannot merely replace lost cells. As first proposed in the 1990s, researchers now know that the pro-inflammatory nature of HIV infection is a key part of disease pathogenesis. Even in early-stage disease, many T cells show an activated phenotype, with the number of activated T cells predicting disease progression independent of viral load.

The cause of this activation is almost certainly the pro-inflammatory cytokines released by activated cells, which can activate other cells and lead to further activation. This process is driven by the release of chemokines and other cytokines, which can activate and recruit additional immune cells to the site of infection. The activated CD4 T cells then undergo proliferation and differentiation, leading to the development of memory T cells and the production of pro-inflammatory cytokines.

Antiretroviral drugs generally used in clinical practice

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)</td>
<td>Tenofovir, abacavir, zidovudine, stavudine, lamivudine, emtricitabine</td>
</tr>
<tr>
<td>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</td>
<td>Efavirenz, nevirapine, etravirine</td>
</tr>
<tr>
<td>Integrase inhibitors</td>
<td>Raltegravir</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>Fosamprenavir, atazanavir, darunavir, lopinavir, saquinavir (ritonavir)</td>
</tr>
<tr>
<td>CCR5 inhibitors</td>
<td>Maraviroc</td>
</tr>
<tr>
<td>Fusion inhibitors</td>
<td>Enfuvirtide</td>
</tr>
</tbody>
</table>

*Some drugs such as zidovudine, stavudine, and nevirapine are generally used in resource-limited regions because of cost considerations. These drugs are generally not recommended as preferred agents in resource-rich regions in view of their potential toxic effects.

Table: Antiretroviral drugs generally used in clinical practice

Antiretroviral drugs and laboratory monitoring

Antiretroviral drugs are classed by the viral life-cycle step they inhibit (figure 1), and in some cases, by their chemical structure. Although many drugs might target a single enzyme, these drugs have unique side-effect profiles, drug-drug interactions, and potency. For those reasons, most formularies allow access to all drugs, but this practice might change once generic drugs become available and the cost differences between therapeutic options become more substantial.

A detailed description of the various antiretroviral drugs is beyond the scope of this Seminar. The table shows drugs that are often used to manage HIV infection, and their most important side-effects and drug interactions. Selected aspects of some of the most widely used drugs are addressed later in this Seminar.

Antiretroviral drug development was substantially accelerated by the development of accurate, reproducible, and inexpensive laboratory tests. By contrast with most diseases that need reductions in mortality or clinical event rates to establish treatment effectiveness, most antiretroviral drugs received accelerated approval on the basis of reductions in HIV RNA concentrations in plasma—the viral load.
CD4 testing
The average CD4 T-cell count in uninfected adults is typically more than 500 cells per μL. Most opportunistic infections and cancers occur as the CD4 T-cell count falls below 200 cells per μL. Recent guidelines use the threshold of 350 cells per μL as a strong indicator for beginning antiretroviral therapy. Since many treated patients have persistent, hence drug-resistant selection is exceedingly rare at persistent viraemia are not clear, viral evolution and set point, but the precise mechanism for these effects remains to be defined. The reasons for set-point variability remain a major focus of HIV research since knowledge about these mechanisms could inform the development of a vaccine or immune-based therapy or as an adjunct to therapy when treatment fails.

Viral load is measured before antiretroviral therapy begins, but its primary value is in monitoring treatment response or failure. The immediate goal of therapy is to reduce HIV replication to a threshold below which the virus does not evolve and drug resistance does not emerge. This exact concentration is unknown, but is probably between 50 and 200 copies of RNA per mL and hence near the lowest range that most assays can routinely detect. For these reasons, the treatment goal is to reduce viral load to undetectable ranges. This simple approach might change as more sensitive assays are developed since many treated patients have persistent, very low viraemia (1–50 RNA copies per mL). Although the source and clinical consequences of this persistent viraemia are not clear, viral evolution and hence drug-resistance selection is exceedingly rare at these very low viral loads.

Drug resistance testing
Antiretroviral drug-resistance mutations will almost invariably emerge if HIV is allowed to replicate in the presence of antiretroviral drug concentrations insufficient to exert complete suppression. The common resistance mutations for all drugs have been well characterised and their detection with reproducible commercial assays is straightforward, as long as the plasma viral load is at least 500–1000 copies per mL. Each antiretroviral drug, and to some degree each drug class, varies in its ability to generate drug resistance. Full resistance to some drugs follows the selection of one mutation—eg, most non-nucleoside reverse transcriptase inhibitors (NNRTIs), lamivudine, and emtricitabine, and perhaps enfuvirtide. By contrast, other drugs retain some activity even after several mutations emerge—eg, most other nucleoside reverse transcriptase inhibitors (NRTIs). The genotypic characterisation of these mutations is now a routine part of clinical management and improves outcome.

Phenotypic assays, which are analogous to antibiotic sensitivity testing, are also sometimes used for patients with more complex disease, but these assays are expensive and less widely available. Resistance assays have many limitations. Most widely available genotypic and phenotypic assays can detect a mutant variant only if it is present in a substantial subset of the circulating virus population (above a prevalence of about 10%). Clinically significant drug resistance often persists as low-concentration minority variants, and hence these variants are not readily detectable with conventional assays. This difficult detection is especially true for individuals who acquired transmitted drug resistance or who have stopped antiretroviral therapy.

Once resistance mutations are selected, they persist indefinitely in infected cells, increasing the risk of treatment failure if the affected drug is used at any later point. This increased risk might not always be the case, however. For example, women who used nevirapine monotherapy to prevent mother-to-child transmission and consequently develop nevirapine resistance might yet respond to this drug if the drug is used after an extended period between the initial exposure and the subsequent initiation of therapy.

Transmission of drug-resistant variants is well described. Although the rates of drug-resistance transmission varies with drug class, the region tested, and the sensitivity of the assay, resistance frequency in most studies is between 5% and 20%. Most guidelines therefore recommend obtaining a baseline genotypic resistance test once HIV infection is diagnosed. During treatment, immediate resistance testing is also strongly recommended if therapy does not fully inhibit viral replication.

Chemokine receptor tropism and HLA-B* testing
HIV enters its preferred target cells by binding to one or both of the chemokine receptors CCR5 and CXCR4 (figure 1). Nearly all patients with primary HIV infection...
Basics of antiretroviral management: when to start treatment

Antiretroviral therapy is best managed by physicians with HIV expertise. The following section outlines generally the state-of-the-art of the most common clinical questions, such as when should therapy be recommended, which drugs should be used first, and when the initial regimen might need changes.

When is the best time to start antiretroviral therapy?
Few issues in the clinical management of HIV infection have generated as intense or extended debates as this question. Such controversy is not surprising in view of the many elements affecting this decision and the rapid developments in the discipline. Early excitement about the potential for three-drug therapy to reduce mortality led to a hit-hard, hit-early approach and even to hopes for a cure.61 This enthusiasm waned when the long-term toxic effects of these regimens were appreciated.62,63 Because of the emergence of better tolerated drugs and evidence that untreated HIV infection is harmful, even during early stage disease, therapeutic strategies are rapidly shifting back to a more aggressive approach. Some guidelines show a philosophical change from waiting as long as possible before starting treatment, to a default approach of starting treatment unless there is a strong reason to defer therapy.64

Debate no longer exists as to when to start treatment in patients with moderate-to-advanced immunodeficiency. The results from observational studies65–67 and from one large randomised clinical trial in Haiti68 provided consistent evidence that therapy should be started soon in all patients presenting with a CD4 T-cell count lower than 350 cells per μL. Treatment should similarly be started promptly in those with an AIDS-defining opportunistic infection or cancer.69

For people with CD4 cell counts higher than 350 cells per μL, the debate is active, although not informed by controlled clinical trials. Results from a large North American cohort study showed a significant mortality benefit of antiretroviral therapy at all CD4 counts,70 even when higher than 500 cells per μL, but data from a largely European cohort study showed no consistent survival benefit above a CD4 count of 350 cells per μL.71 Since both cohort studies have methodological limitations, much of the discussion about when to start antiretroviral therapy has focused on emerging appreciation of the potential harm of untreated HIV infection and increasing evidence that present therapeutic options are safe. The key arguments in this discussion are potency, expense, toxic effects, convenience, adherence forgiveness, damage of untreated HIV infection, and prevention of transmission with antiretroviral therapy.

In terms of potency, present antiretroviral regimens in treatment-naïve people suppress plasma viral loads below assay detection limits in over 90% of clinical trial participants.62,63,74 These impressive success rates are often also seen in real world clinical use. Once viraemia is controlled for 1–2 years, virological failure is uncommon.

The cost for most combination regimens approaches $12 000 yearly. Despite this expense, antiretroviral therapy is generally seen as cost effective, at least compared with other therapeutic strategies generally used.75 In many resource-rich regions, treatment is subsidised by public funding. There is genuine concern, however, that even in these countries, full and continuous access to antiretroviral therapy could be threatened by weak economies. Long waiting lists for access to publicly supported treatment programmes exist in many states within the USA, and these lists seem to be getting longer. Generic versions of drugs with a solid safety and effectiveness record—eg, lamivudine and saquinavir—will soon become widely available. The effect of generic drugs on formularies and drug prices is unknown.

Toxic effects are also important. All the widely used antiretroviral drugs are well tolerated and safe, but none are wholly benign. The mechanism accounting for many of the most important toxic effects that are generally seen during therapy remains undefined. This is especially true for peripheral fat wasting (lipoatrophy) and central fat accumulation (lipohypertrophy).76 These potentially disfiguring body changes can cause stigma and might be a major reason why some individuals delay or stop therapy.

Of the NRTIs, tenofovir can cause renal toxic effects and potentially osteopenia.77 Abacavir can cause an increased risk of cardiovascular events78 and is associated with a serious hypersensitivity reaction in patients who are HLA-B*5701 positive.79 Many of the once popular thymidine analogues, particularly stavudine, were also thought to be benign, but are now known to cause profound long-term and probably irreversible side-effects such as lipoatrophy.80 Fears of unknown long-term toxic effects remain one of the
strongest arguments for deferring therapy for people with very early disease.

For NNRTIs, efavirenz is teratogenic\(^7\) and should be avoided in women who are or might become pregnant. Efavirenz also has substantial short-term CNS toxic effects. Nevirapine—which remains the cornerstone for most regimens worldwide because of its low cost—can cause substantial liver toxic effects and hypersensitivity reactions. These reactions typically arise within the first few weeks of therapy. For unclear reasons, nevirapine-associated toxic effects are common in patients starting therapy with high CD4 T-cell counts. Nevirapine is hence generally not recommended for women who have a CD4 T-cell count higher than 250 cells per \(\mu L\) or men who have a CD4 T-cell higher than 400 cells per \(\mu L\).\(^5\)

With respect to integrase inhibitors, raltegravir is safe, well tolerated, and highly effective but long-term safety data are missing. Most protease inhibitors can increase plasma lipid concentrations, potentially increasing cardiovascular risk,\(^7\) and many have clinically relevant drug interactions, especially when low doses of ritonavir are used to boost the pharmacological profile. Most of these drugs are associated with gastrointestinal disturbance. Atazanavir raises the plasma concentrations of unconjugated bilirubin and occasionally causes reversible jaundice.

Of the CCR5 inhibitors, maraviroc is generally well tolerated and has no known short-term or long-term side-effects. By contrast with other drug classes, CCR5 inhibitors bind to a host rather than a virus target, and hence could carry more long-term risk. The drug probably has an immunomodulatory effect, as defined by rapid increase in CD8 T cells. The rare individuals who lack CCR5 generally do well, but are at increased risk of developing more severe clinical symptoms when infected with West Nile virus.\(^8\) This finding has led to a concern that therapeutic inhibition of CCR5 could have uncommon but potentially severe consequences. Enfuvirtide, as a fusion inhibitor, is expensive and generally poorly tolerated because of the need for injections twice daily that often cause painful local subcutaneous reactions. The drug is only used in patients with no other options.

In terms of convenience, the most popular regimen is a coformulation of three drugs in a single pill taken once daily (tenofovir, emtricitabine, efavirenz). Most other first-line regimens can be taken once daily. Inconvenient dosing regimens are no longer a major treatment barrier, especially for first-line therapy.

Strict drug adherence is needed to achieve and maintain viral suppression. Suboptimum exposure to some drugs can result in the rapid development of drug resistance (low genetic barrier). This rapid development is especially true for some of the more popular first-line drugs—eg, lamivudine, emtricitabine, nevirapine, efavirenz, and perhaps raltegravir. Other drugs such as protease inhibitors typically have a high genetic barrier and hence need long-term exposure before resistance emerges; these drugs are believed to be more forgiving in terms of non-adherence. Complicating these issues is the fact that although some drugs might be susceptible to resistance development, their very long half-life in vivo protects the drug from frequent missed doses. The impressive activity of efavirenz might be attributable to a long steady-state half-life. The degree to which these issues should affect treatment decisions remains controversial.

The damage of untreated HIV infection should also be considered. Previous debates about when to start therapy were largely based on the comparison of the risk of drug toxic effects with the risk of developing AIDS and AIDS-related mortality. The present debate has shifted to include the potential toxic effects of uncontrolled HIV replication in patients with early-stage disease. In one large study of continuous versus intermittent antiretroviral therapy, the group randomised to intermittent treatment had a higher rate of non-AIDS morbidity, including cardiovascular disease, cancer, kidney disease, and liver disease.\(^8\) Cohort studies suggest HIV-associated damage is accelerated in many organ systems, raising the possibility that several non-AIDS complications could be delayed or avoided by starting antiretroviral treatment earlier. Bone, renal, hepatic, cardiovascular, and neurocognitive functions all seem to be adversely affected by sustained HIV replication, advancing immunodeficiency, or both,\(^4\) although the specific mechanism remains uncertain and the data are sometimes inconsistent.\(^0,7\)

A final issue, also actively debated, is the possibility that treatment of a much larger portion of the HIV-infected population than at present will alter the epidemic’s transmission dynamics. Antiretroviral therapy during pregnancy essentially prevents all mother-to-child transmission,\(^8\) and additional data suggest that treatment-mediated viral suppression results in striking reductions in sexual transmission of HIV.\(^8\) Community-wide data and mathematical models suggest that increase of antiretroviral therapy in a community results in a reduction in the number of transmission events and hence in the overall size of the epidemic.\(^9\) In view of the cost of HIV therapeutics, any approach that reduces the number of infected people could be profoundly beneficial in terms of resource allocation.\(^0\)

When should treatment be started? On the basis of these factors, some have argued that treatment options that are currently available are probably less toxic than sustained viral replication. Conversely, antiretroviral drugs are expensive, have to be taken daily (which could be a constant reminder to some that they have a chronic disease), and might have as yet unknown toxic effects. Also, the absolute benefit of treatment in patients with early-stage disease is probably not large, provided that treatment is not deferred until more advanced stages of disease (less than 350 cells per \(\mu L\)).

The various national and international guideline panels have made some striking and at times confusing changes
as to when to start treatment—more so now than in the past. Currently, all panels recommend treatment for individuals with a CD4 T-cell count lower than 350 cells per μL. These recommendations are shared between resource-rich and resource-poor regions. Perhaps indicating different regional perspectives, the US-based Department of Health and Human Services panel recommends treatment for nearly all patients, whereas British and European guidelines generally recommend therapy only for patients with CD4 cell counts lower than 350 cells per μL and for selected patients such as those with active viral hepatitis or coronary artery disease. Randomised trials of early versus deferred treatment in resource-poor regions. Perhaps with active viral hepatitis or coronary artery disease. These recommendations are shared between individuals with a CD4 T-cell count lower than 350 cells per μL. These recommendations are shared between the various therapeutic options have to be made. Much of the art of modern HIV medicine is the effective tailoring of these choices to a particular individual’s expectations and needs.

All currently recommended treatment regimens consist of a backbone of two NRTIs and a third drug. This strategy largely shows the way in which therapy was introduced over the past 15 years, with the standard of care evolving from the use of one NRTI to two NRTIs to a combination of two NRTIs and a third drug. Most subsequent clinical trials have used the two NRTI plus a third drug approach. Regimens that do not include an NRTI backbone could represent the next major shift in treatment approaches, but these regimens are just now starting to be considered.

The most popular NRTI combination is tenofovir with emtricitabine. In resource-rich regions, these two drugs are coformulated as a single once-a-day regimen. Abacavir with lamivudine is also a once daily coformulated combination in some regions but abacavir needs screening for hypersensitivity risk, has potential cardiovascular side-effects, and might be less effective than tenofovir. Lamivudine and the closely related emtricitabine are safe, well tolerated, once-a-day drugs that are included in all first-line regimens and in most subsequent regimens. The drugs are potent against wild-type virus and even have residual activity against resistant viruses.

The third anchor drug that is paired with two NRTIs is typically either an NNRTI, a ritonavir-boosted protease inhibitor, or an integrase inhibitor. Ritonavir is an inhibitor of HIV protease, but is also a potent inhibitor of the P450CYP3A enzyme, and is typically used at low doses to boost the concentrations of other protease inhibitors, since most are heavily metabolised by the P450 system. Within the protease inhibitor class, atazanavir, lopinavir, and darunavir—all boosted with low-dose ritonavir—are the most popular, although other effective options are available.

With respect to the NNRTI option, efavirenz is the most popular because it is highly potent and is available in some regions as a one-pill-once-a-day combination regimen (the

Panel: Unanswered questions about HIV therapeutics

• When is the best time to start antiretroviral therapy?
• Is the harm associated with untreated HIV infection greater than the harm associated with exposure to present therapeutic regimens?
• Is the immunodeficiency associated with progressive disease wholly reversible with therapy?
• Is the current generation of drugs sufficient to provide most people with the ability to maintain suppression over the next several decades, or will a renewed effort at antiretroviral drug development eventually become necessary?
• Can the newest and potentially most effective therapeutic options, now widely available in resource-rich regions, become more cost effective and hence available worldwide?
• Are viral load measurements necessary and cost effective for the management of treatment in resource-poor regions?
• What role, if any, does persistent inflammation and residual immunodeficiency have in causing premature heart disease, kidney dysfunction, liver disease, bone disease, and neurocognitive decline?
• What role will there be in treated patients for adjunctive immune-based therapeutics in either restoration of immunological function or reduction of inflammation?
• Is there a reasonable regulatory pathway for the development of such drugs?
• Will the notion of the use of two nucleoside analogues and a third anchor drug in first-line regimens ever be successfully challenged?
• Will the potential long-term toxic effects of even the safer nucleoside analogues—particularly tenofovir and abacavir—only definitely emerge after decades of exposure?
• What role, if any, does continuing viral replication have in explaining HIV persistence in patients who are otherwise doing well on antiretroviral therapy?
• Does treatment-mediated reduction of viraemia in blood wholly prevent the capacity of an infected person to transmit HIV to his or her sexual partner?
• Will earlier use of antiretroviral therapy on a community level reduce the rates of HIV transmission in that community?
• Can short exposure to therapy before or after a sexual exposure prevent HIV acquisition?
• Can HIV be cured?
coformulated efavirenz, tenofovir, emtricitabine). The main limitations of efavirenz are its short-term CNS toxic effects and its established teratogenicity. Nevirapine can be less potent and more toxic than efavirenz.96 Interest in the integrase inhibitor raltegravir is strong, but it is only approved for a twice daily dosing.

When to switch treatment
When should therapy be changed and what should be given after the first-line antiretroviral drug regimen? Initial HIV therapy is expected to succeed. Most treatment modifications result from toxic effects and to identify and replace the drug that is causing the unwanted side-effect is generally straightforward.94 Although uncommon, more serious versions of treatment failure can happen and the various types of therapeutic failure have their own causes and consequences.

Virological treatment failure is generally defined as persistently detectable plasma HIV RNA concentrations after 16–24 weeks of therapy. Nearly all first regimen virological failures can be attributed to non-adherence or pre-existing drug resistance.51 Virological failure should trigger a thorough review of drug side-effects (a common cause of non-adherence5) and a search for other drugs that could be affecting absorption or metabolism. Because resistance selection might have occurred, a resistance genotype should be obtained.46 The regimen should be modified quickly with the goal of giving at least two, and preferably three, drugs to which the virus remains fully sensitive. Any regimen change should be accompanied by a carefully devised plan to monitor side-effects and adherence. In view of the number of therapeutic options, the capacity of second-line and perhaps even third-line regimens to achieve and maintain viral suppression has improved substantially in the past few years.98–100

Compared with virological failure, immunological treatment failure is less easily defined but might be said to arise when CD4 recovery is inadequate to protect the patient against AIDS and non-AIDS-related morbidity. Since there is probably no CD4 T-cell count below the normal range that is truly safe, the optimum immunological outcome seems to be sustained CD4 T cell in the normal range (more than 500 cells per μL).101 Immunological failure is most common when treatment begins at a very advanced disease stage—eg, a CD4 cell count lower than 200 cells per μL.5,102 Old age also increases the risk of immunological failure.103,104 Since a low CD4 T-cell count on treatment is associated with an increased risk of various AIDS and non-AIDS events,30,105 identifying novel therapeutic interventions for this subset is a major focus in clinical investigations. The immunological agent interleukin 2 was ineffective in two very large trials.32

Present translational research themes
The last 15 years of HIV clinical research have largely focused on development of effective strategies for suppression of HIV replication in a durable and safe manner. The clinical research agenda is now shifting toward addressing a new set of questions, as outlined below and in the panel.
1–50 copies per mL, which are detectable with highly sensitive research assays (figure 2A).1 The slow release of non-infectious virus particles from longlived cellular reservoirs probably explains much of this persistent viraemia.109,114 One of the most controversial issues in the specialty is whether very low-level viral replication also contributes to viral persistence, with some evidence to support either side of the debate.110–113 Even if low-level replication is continuing, it is clearly insufficient to sustain systemic evolution and drug-resistance selection.114 Regardless of its root cause, HIV persistence during the normal range (figure 2B).5,115,116 Since this carries a reach an apparently stable plateau that is well below the normal range (figure 2B).5,115,116 Since this carries a risk, determination of its cause is very important. Factors known or postulated to limit full CD4 cell recovery are old age,4 the presence of co-infections such as hepatitis C virus, a lower pretreatment CD4 T-cell nadir,1 injection drug use,115 persistent microbial translocation,117 high-level T-cell activation,118 lymphoid fibrosis,119 and perhaps the presence of specific HIV populations—eg, subtype D virus or X4 virus.120

The clinical response to therapy is also highly variable. For example, some patients who begin treatment during advanced HIV infection have a severe paradoxical AIDS-defining event, even as they have an apparent virological and immunological response to therapy. This immune reconstitution inflammatory syndrome (IRIS) is unpredictable, has no clear mechanism or treatment, and can be life-threatening.

Does HIV infection accelerate the normal ageing process or is it a new risk factor for end-organ damage (figure 3)? Many reports and widespread clinical experience document a higher frequency of organ-specific disease in HIV-infected adults than is expected in uninfected age-matched controls. Cardiovascular disease,120,121 bone disease,122,123 cancer,124,125 renal impairment, and perhaps neurocognitive deficits126 might be more common in HIV-infected individuals than in age-matched controls. Some studies even record a prefrailty syndrome at higher than expected rates in patients who take antiretroviral drugs.127 Although some of these effects might suggest toxic effects for antiretroviral drugs, or higher frequency of traditional risk factors, HIV-associated inflammation—which is not fully reversed by therapy—might be a contributing factor (figure 3).128 This multisystem array of comorbid illness might resemble an acceleration of the normal ageing process.129,130

Perhaps the strongest evidence that HIV infection causes accelerated ageing comes from focused studies on immune function. Ageing of the immune system is associated with reduced numbers of naïve and central memory T cells, reduced T-cell regenerative capacity, increased numbers of well differentiated T cells, and increased inflammation. These trends are generally referred to as immunosenescence.131 Untreated HIV infection seems to cause many of these same changes, and effective antiretroviral therapy—especially when started late in the disease process—fails to restore immunological health.132

Another, not necessarily exclusive, possibility is that HIV infection represents a new risk factor for end-organ disease which, when combined with other risk factors, lowers the age at which these disease phenotypes develop. Thus, HIV replication or HIV-associated immune dysfunction could cause accelerated cardiovascular disease, especially against a background of genetic risk and an increased rate of traditional risk factors. Similarly, HIV-associated neurocognitive disorder is common even in those with suppressed HIV plasma viraemia and is the subject of a substantial research effort.133 It is more common with advanced age and has been associated with intrathecal immune activation.134 Definition of the cause(s) of premature non-AIDS morbidity is of crucial importance because it will clearly define clinical research and management strategies.

Does antiretroviral therapy have a role in decreasing transmission at individual and community level? Several community surveys have identified an association between decreases in the median HIV viral load and rates of HIV incidence or diagnosis.135 In individuals, HIV suppression prevents transmission from infected women to their newborn babies,136 and sexual transmission in serodiscordant adults is reduced in those with lower viral loads in the absence of antiretroviral therapy.137 These findings suggest the possibility of HIV treatment as a part of transmission prevention.138 This possibility is being explored in a prospective trial, as is another strategy in which uninfected people
engaging in risk behaviours receive chronic antiretroviral therapy to prevent HIV acquisition.

Can HIV infection be cured? The life-cycle of HIV needs permanent integration of the virus’s genetic information into the host chromosomes. HIV preferentially targets CD4 T cells. Although most infected cells seem to die rapidly, a small proportion reverts to a resting memory phenotype that harbours HIV DNA. Since these cells are some of the longest-lived cells in the body, HIV infection can persist for decades in a dormant stage that is inaccessible to the immune system or present antiretroviral therapy.109–111

Although present treatments are fully effective at infected cells die.109 suggests that it might take decades before all previously long-lived nature of the so-called latent reservoirs preventing de-novo infection of new target cells, the happens in clinical practice.144 In a study of patients who unquestioned, multidrug (six-class) resistance still options. Although the success of new drugs is sharply reduced their investment in new therapeutic salvage drugs, the pharmaceutical industry has substantially. Because of the absence of a clear market for regimens are few.146 A slow but consistent rate of multidrug resistance HIV development could theoretically lead to a large epidemic over the next decades in a dormant stage that is inaccessible to the death of the infected cells) or drugs that possibly approaches are being considered, including the use of drugs that activate DNA transcription (which could force the production of HIV virions and the death of the infected cells) or drugs that preferentially activate the immune system (which could force a longlived memory cell to become a shortlived effector cell). Other approaches include gene therapy to reconstitute the immune system with T cells not susceptible to HIV infection. A reported case of HIV being eradicated in a patient after an allogeneic stem-cell transplant from a donor genetically lacking CCR5 gives fresh momentum to the pursuit of a cure.141

Will there be a large epidemic of drug-resistance HIV in the future? In view of the recent development of various well tolerated drugs that are highly effective against viruses that developed resistance to the first generation of antiretroviral drugs, the number of individuals with difficult-to-treat multidrug-resistant HIV has declined substantially. Because of the absence of a clear market for new salvage drugs, the pharmaceutical industry has sharply reduced their investment in new therapeutic options. Although the success of new drugs is unquestioned, multidrug (six-class) resistance still happens in clinical practice.140 In a study of patients who were managed in the modern era, about 9% showed evidence of virological failure to at least three drug classes over 10 years.140 Higher than expected rates of resistance emergence are being seen in some African cohorts, in which therapeutic options for second-line and third-line regimens are few.140 A slow but consistent rate of multidrug resistance HIV development could theoretically lead to a large epidemic over the next several years or decades. The absence of continuing drug discovery could eventually prove to be a major drawback to successful treatment.

Conclusion

HIV is now a chronic illness in patients with continued treatment access and excellent long-term adherence. Similar success is being realised in even desperately poor settings. Although the success of therapy is unquestioned, many issues persist. Since cure is not yet possible, treated people have to maintain lifelong adherence and face the risk of delayed drug toxic effects. Even treated HIV infection might cause chronic low-level inflammation with its potential for harm, incompletely restored immune function, and a higher than expected risk for many complications often associated with ageing. Perhaps most importantly, we confront a growing recognition that many health-care systems might exhaust the resources needed for effective HIV care. The fact that HIV drug development has declined raises further concerns that therapeutic options might not be available over the next decades for those who cannot tolerate or whose disease does not respond to present options. A concerted scientific research effort is needed to maintain the unprecedented progress in HIV therapy, but this effort will need to be understood and supported by political leaders if the epidemic is to be truly controlled.

Contributors

Both authors contributed equally to the conception, drafting, and editing of this Seminar.

Conflicts of interest

PAV has served as a scientific advisor to Bristol-Myers Squibb, Gilead, Pfizer, and Tobra. He serves on data safety monitoring boards for Merck and TanMed and formerly on an endpoint adjudication committee for Schering Plough. SGD has received research grant support from Merck, Bristol-Myers Squibb, and Gilead and has served as a scientific advisor to Tobra.

Acknowledgments

This work was supported in part by the UCSF-Gladstone Institute of Virology and Immunology Centers for AIDS Research (PO AI027763) (PAV, SGD). Additional support was provided by the NIH (AI08745, AI069994) (SGD). We thank Warner Greene for permission to use figure 1, John C W Carroll for assistance with graphic design, and Parn Derish for copy editing assistance.

References


14 Popovic M, Sarnagahzaran MG, Read E, Gallo RC. Detection, isolation, and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS. Science 1984; 224: 497–500.


Seminar


137 Dieffenbach CW, Fauci AS. Universal voluntary testing and treatment for prevention of HIV transmission. JAMA 2009; 301: 2380–82.


142 Fauci AS, Folkers GK. Investing to meet the scientific challenges of HIV/AIDS. Health Aff (Millwood) 2009; 28: 1629–41.


