Antiretroviral therapy and management of HIV infection

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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.

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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.[1,2] 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.[3–5]

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.[6–8] This short life expectancy is especially true for patients who initiate therapy during advanced stages of their disease,[6] but might even be true for optimally treated patients.[9] 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 expected to become a major disease burden in the many regions where these drugs are still used. Many patients cannot maintain the high levels of adherence necessary for virus control, and, worldwide, large populations do not have continuous access to treatment. International programmes providing antiretroviral drugs to resource-limited countries are reaching only a proportion of those needing care and are threatened by the present economic downturn and changes in political will. There also remains the real possibility that recently developed drugs, currently assumed to be safe, will show novel side-effects after long-term use. Finally, many HIV-infected people remain unaware of their HIV infection, continue to transmit HIV to others, and when diagnosed have very advanced and often difficult-to-treat late-stage disease. These concerns are especially relevant to the most marginalised communities who are disproportionately affected, even in resource-rich countries such as the USA.[10]

This Seminar briefly reviews the natural history and pathogenesis of antiretroviral untreated and treated HIV disease, the drugs used to treat the infection, and the tests used to monitor care. The unmet treatment needs are discussed in detail. Although the primary focus is on care in settings in which economics slightly constrain resources, the unique needs and challenges associated with the worlwide roll-out of antiretroviral drugs are also addressed.

Initial epidemic and early response

The simian version of HIV was probably transmitted from its natural host, the chimpanzee, to man in the early to middle years of the 20th century in the west central African countries of Cameroon and Gambia.[11] The spread of HIV in man was initially slow and focal, but became explosive because of rapid urbanisation in the post-colonial era. Shortly after gaining a deeper hold in African cities, HIV rapidly spread worldwide, appearing in at-risk individuals in most regions by the mid-to-late 1970s.

HIV infection was unrecognised in medical publications until the clinical syndrome of advanced immune

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.[12] HIV was first cultured in 1983 and rapidly established as the causative agent of AIDS.[13,14] 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).

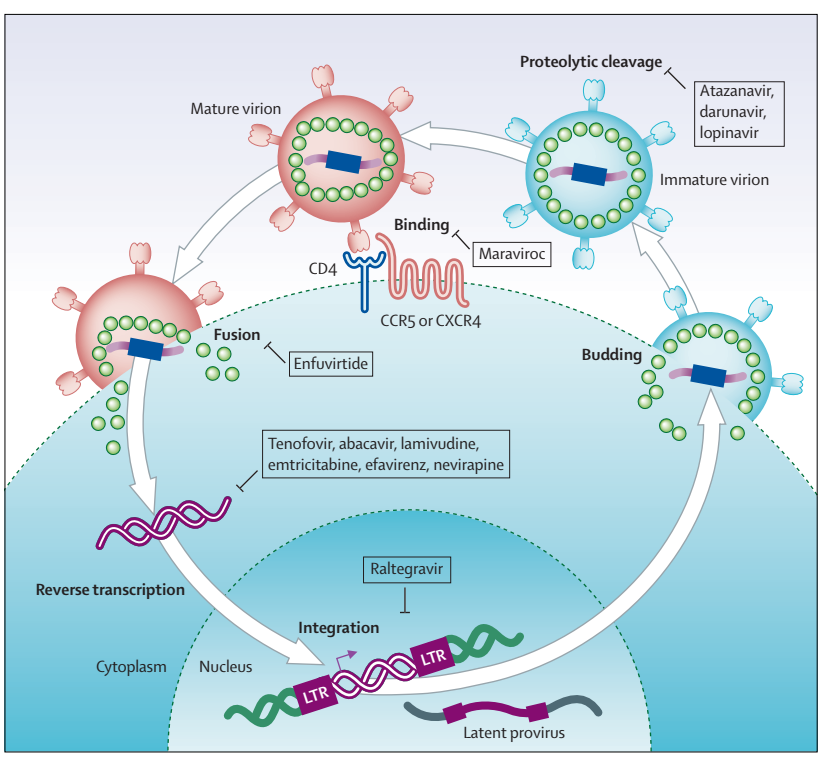

Figure 1: **HIV life cycle and antiretroviral drug targets**
Present antiretroviral drugs span six classes that target five unique steps in the HIV life cycle (binding, fusion, reverse transcription, integration, and proteolytic cleavage). The most common drugs used in resource-rich regions to target 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 enfurvitide 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.

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.[15] 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.[16,17] 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.[16,18] 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.[19] Since this symptom complex is not specific, acute infection is often unrecognised. 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.[20]

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.

	Drugs	Comments
Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)	Tenofovir, abacavir, zidovudine,* stavudine,* lamivudine, emtricitabine	Tenofovir is associated with renal and perhaps bone dysfunction. Abacavir is associated with hypersensitivity reactions in at risk individuals (HLA B5701) and is associated in some studies with an increased risk of cardiovascular disease. Abacavir might be less potent than tenofovir in patients with high viral loads. Zidovudine and stavudine are associated with profound fat redistribution (lipoatrophy). All NRTIs are associated with potential to cause risk of severe lactic acidosis. The combination of tenofovir and emtricitabine is the preferred first-line regimen in most regions
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz, nevirapine,* etravirine	Efavirenz can cause CNS toxicity (which is usually time limited). Efavirenz has teratogenic potential and should be used with caution in woman who might become pregnant. Nevirapine can cause severe hepatoxicity when used in patients with higher CD4 cell counts (more than 250 cells per μL for women and more than 400 cells per μL for men). Etravine is given twice daily and has generally been used as second-line regimen
Integrase inhibitors	Raltegravir	Raltegravir has no short-term and no known long-term toxic effects, although data are scarce
Protease inhibitors	Fosamprenavir, atazanavir, darunavir, lopinavir, saquinavir (ritonavir)	Most protease inhibitors are extensively metabolised by the P450 CYP3A system; ritonavir is generally given at low doses (100–200 mg per day) to inhibit P450 and boost the co-administered protease inhibitors. Most protease inhibitors are associated with hyperlipidaemia and other metabolic abnormalities such as insulin resistance. Long-term protease inhibitor exposure has been associated with increased risk of cardiovascular disease
CCR5 inhibitors	Maraviroc	Maraviroc is only active in patients who do not have virions that use CXCR4 for cell entry. A specialised assay is therefore needed to screen for coreceptor tropism. By contrast with other antiretroviral drugs, maraviroc binds to a host rather than a viral target. Maraviroc has an immunomodulatory effect that is independent of its effect on HIV replication; the clinical significance of this activity is unknown.
Fusion inhibitors	Enfuvirtide	Enfuvirtide must be given subcutaneously twice daily and is very expensive. The drug is generally used only in patients with no other therapeutic options

*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**

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.[21,22] As first proposed in the 1990s,[23] researchers now know that the pro-inflammatory nature of HIV infection is a key part of disease pathogenesis.[24,25] Even in early-stage disease, many T cells show an activated phenotype,[26,27] with the number of activated T cells predicting disease progression independent of viral load.[27,28] The cause of this activation is almost certainly multifactorial, and includes the direct effects of HIV infection, HIV-mediated destruction of the mucosal barriers (which results in chronic translocation of microbial products from the gut lumen into the systemic circulation),[29] and the damage of the thymus and other lymphoid tissues (which can result in the expansion of proinflammatory co-infections such as cytomegalovirus).[22,26,30] Chronic inflammation probably drives disease progression by increasing the number of susceptible CD4 target cells, increasing the turnover and eventual exhaustion of uninfected T cells, altering the function of these cells and other important components of the immune system, and directly damaging the vascular endothelium and other tissues.[21,31] Although long-term suppression of HIV replication with antiretroviral therapy prevents much of this process, it does not fully restore immunological health. Persistent inflammation during treatment—and its effect on various organ systems such as the cardiovascular system—remains one of the major limitations of present therapeutic strategies. Although efforts continue, no treatment directed at HIV immunopathogenesis has proved to have clinical value.[32]

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.[33]

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.[34–36] This threshold was selected, in part, because it was midway between the lower limit of normal (500 cells per µL) and the threshold often used to define AIDS (200 cells per µL). Data from some, but not all, cohorts suggest that this threshold of 350 cells per µL could be close to the threshold at which the benefits of starting therapy clearly outweigh the risk of delaying treatment (see below for a detailed discussion about when to start therapy).[37,38] Once treatment has begun, CD4 T cells typically increase rapidly for the first 3 months and then slowly increase by roughly 50–75 cells per µL per year, with rates declining as the CD4 T-cell count reaches normal.[3] The biological and assay variability of the peripheral CD4 cell count is high, making it difficult to rely on one measurement.

Quantitative viral load testing

Quantitative viral load, or concentrations of plasma HIV RNA, is measured with PCR or related methods. Chronic established HIV infection is often associated with a stable set point, which varies widely between individuals. The viral load set point is associated with the rate of CD4 T-cell decline and with the risk of AIDS and death.[39,40] Both virus and host factors contribute to the viral load set point,[41,42] 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[43] since many treated patients have persistent, very low viraemia (1–50 RNA copies per mL).[44,45] 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.[46,47] 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).[48] The genotypic characterisation of these mutations is now a routine part of clinical management and improves outcome.[46,49] 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.[46] 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.[50–52]

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.[53] 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[54,55] 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.[56]

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%.[57–60] Most guidelines therefore recommend obtaining a baseline genotypic resistance test once HIV infection is diagnosed.[38,40] 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

harbour a virus that binds to CCR5 (R5 virus), thus termed R5 virus. For unclear reasons, as the disease progresses over time, many, if not most, untreated individuals develop a virus that also binds to CXCR4 (X4 virus).[61] Since one therapeutic drug class specifically targets CCR5 (table), testing is needed to define which tropism of the virus (CCR5 *vs* CXCR4) is present.[35] The only validated tropism assay is an expensive phenotypic test that takes 2–4 weeks and is done only in a few specialised laboratories.[46] In view of these limitations, genotypic tropism assays are being developed and might gain widespread use.

Abacavir is an NRTI that is widely used despite some limitations.[62,63] It causes severe hypersensitivity reaction in 5–9% of exposed individuals. This risk is closely related to the presence of the class I HLA allele HLA-B*5701. Testing for this allele is recommended before beginning the drug.[35,64]

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 therapy should 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.[65] This enthusiasm waned when the long-term toxic effects of these regimens were appreciated.[66,67] 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.[35]

Debate no longer exists as to when to start treatment in patients with moderate-to-advanced immunodeficiency. The results from observational studies[37,38,68,69] and from one large randomised clinical trial in Haiti[70] 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.[71]

For people with CD4 cell counts higher than 350 cells per µL, and even those with counts higher than 500 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,[37] 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.[38] 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-naive people suppress plasma viral loads below assay detection limits in over 90% of clinical trial participants.[62,72–74] 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 (lipohypertophy).[66] 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.[76] Abacavir can cause an increased risk of cardiovascular events[63,76] and is associated with a serious hypersensitivity reaction in patients who are HLA-B*5701 positive.[64] 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.[77] 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[78] 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 µL or men who have a CD4 T-cell higher than 400 cells per µL.[35]

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,[79] 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.[80] 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, efavirez). 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.[81] 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,[82–85] although the specific mechanism remains uncertain and the data are sometimes inconsistent.[86,87]

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,[88] and additional data suggest that treatment-mediated viral suppression results in striking reductions in sexual transmission of HIV.[89] 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.[90] 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.[90]

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 µL).

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.[34–36,91,92] These recommendations are shared between resource-rich and resource-poor regions.[91] Perhaps indicating different regional perspectives, the US-based Department of Health and Human Services panel recommends treatment for nearly all patients,[35] 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.[91,92] Randomised trials of early versus deferred treatment in patients with early-stage disease are in progress.

What treatment to start

What drugs should be used in an initial antiretroviral regimen? Several well tolerated and highly effective regimens are available for treatment-naive patients. The differences in terms of virological outcomes for the available regimens are often subtle and need very large studies to discern them.[62,72,74,93] Convenience, pill burden, tolerability, and long-term toxic effects are now the most important factors to consider when decisions 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.[94]

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.[72]

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,[52] has potential cardiovascular side-effects,[63] and might be less effective than tenofovir.[62] 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.[34,35] The drugs are potent against wild-type virus and even have residual activity against resistant viruses.[95]

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?

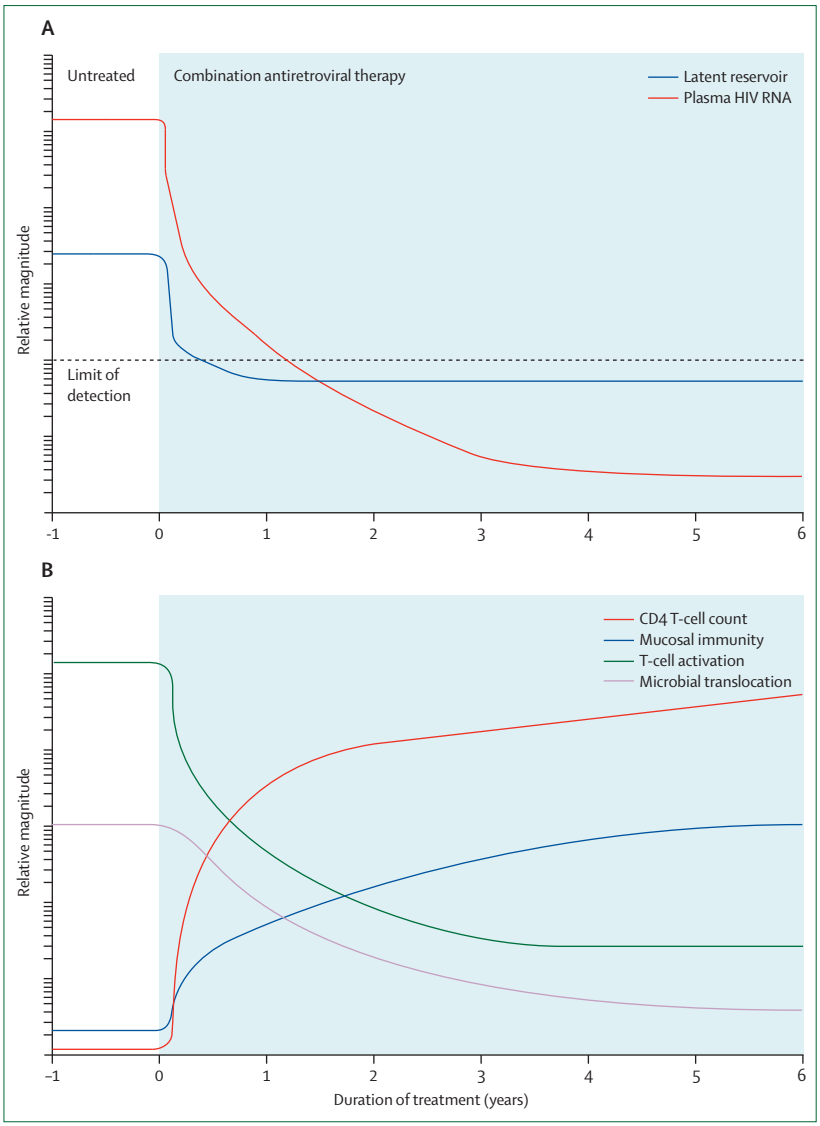

Figure 2: **Virological and immunological responses to combination antiretroviral therapy**
(A) Combination antiretroviral therapy typically results in greater than 100-fold decrease in circulating HIV RNA during first 2 weeks of treatment, which is followed by a slow but measurable decline over time, with a new very low steady-state often being reached after several years of therapy. The level of the latent reservoir—defined as long-lived cells containing replication competent HIV—declines as well, although the kinetics are less striking. (B) Treatment-mediated suppression of HIV replication is associated with sustained but variable increases in peripheral and mucosal CD4 T-cell counts, with the former more often achieving normal values after several years of therapy. T-cell activation, inflammation, and microbial translocation also improve but rarely fully normalise during long-term therapy.

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-adherence[97]) 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,[105–108] 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.

What explains the variable outcomes in patients given antiretroviral drugs? The goal of therapy is to reduce plasma HIV RNA concentrations to below values that are detectable with commercially available assays, generally around 50 copies per mL. Most patients achieve this goal but continue to have HIV RNA concentrations of

1–50 copies per mL, which are detectable with highly sensitive research assays (figure 2A).[45] The slow release of non-infectious virus particles from longlived cellular reservoirs probably explains much of this persistent viraemia.[109,110] 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 therapy might cause chronic inflammation, persistent immunodeficiency, and raised risk for organ damage.

The long-term immunological response to therapy is also highly variable. Although the typical patient shows a sustained CD4 cell increase,[3] many treated patients 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 some co-infections such as hepatitis C virus, a lower pretreatment CD4 T-cell nadir,[5] 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.[116]

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 deficits[126] 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).[31,128] 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 naive 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]

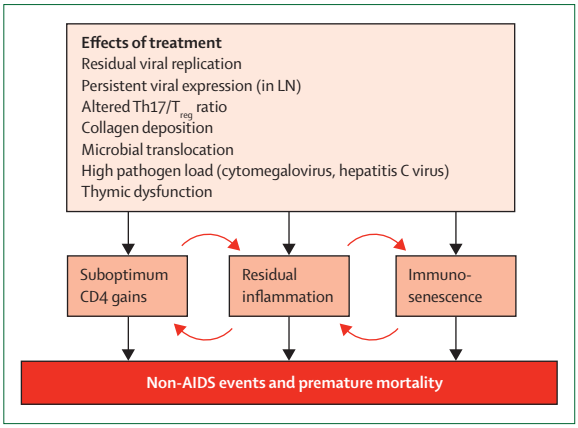

Figure 3: **Pathogenesis of non-AIDS morbidity and mortality during treatment**
Chronic inflammation during therapy is associated with persistent inflammation and immune activation, which in turn is associated with and presumably causally related to higher than expected risk of premature heart disease, kidney disease, liver disease, bone disease, cancer, and neurocognitive dysfunction.

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 genotypic 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,[88] and sexual transmission in serodiscordant adults is reduced in those with lower viral loads in the absence of antiretroviral therapy.[136] These findings suggest the possibility of HIV treatment as a part of transmission prevention.[89,90,137,138] 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.[139–141] Although present treatments are fully effective at preventing de-novo infection of new target cells, the longlived nature of the so-called latent reservoirs suggests that it might take decades before all previously infected cells die.[109]

In view of the absence of an effective HIV vaccine, and because therapy is both expensive and unable to fully restore health, there is a growing consensus that a focused effort on eradication of HIV from its protected reservoirs should be investigated.[142] Some possible 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.[143]

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.[144] 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.[145] 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.[146] 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 Tobira. He serves on data safety monitoring boards for Merck and TaiMed 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 adviser to Tobira.

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