Antiretroviral treatment of HIV infected adults

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It has been about 10 years since the first report that three drug combination antiretroviral therapy can durably suppress HIV replication.¹ Subsequent studies have confirmed that when used appropriately highly active antiretroviral therapy can suppress viral replication to such low levels that the virus is unable to generate drug-resistance mutations. Theoretically, once this level of viral suppression is achieved, treatment should work indefinitely, and the long term risk of morbidity and mortality related to HIV associated immunodeficiency becomes negligible. Experience to date suggests that lifelong suppression of HIV is feasible.

This review is aimed at informing clinicians about the current management of HIV infection. Authoritative and continuously updated reviews are available on the web (for example, the US Department of Health and Human Services treatment guidelines at www.hivatis.org); this review does not attempt to exhaustively summarise the literature or to provide guidance to clinicians with expertise in HIV. Rather, I summarise those issues that are likely to confront clinicians, including those who do not routinely treat people infected with HIV.

Sources and selection criteria

I searched PubMed databases for studies pertaining to antiretroviral therapy and its complications, lipodystrophy and lipoatrophy, and immune reconstitution. I also consulted recently published national and international treatment guidelines and considered unpublished data presented at international meetings.

What is the goal of therapy?

HIV seems to be designed to mutate and evolve as rapidly as possible. This evolutionary capacity is the result of at least three properties: an extremely high rate of virus turnover (at least 10^{10} new virions are produced per day), a high mutation rate (about one mutation per new virion), and an impressive capacity of many HIV proteins to function in the face of multiple amino acid changes.

Theoretical considerations predict that the only manner in which to ensure long term effectiveness of therapy is to durably suppress replication to below the threshold necessary for systemic HIV evolution. Clinical experience suggests that this threshold is likely at or near the level of HIV RNA quantification with most viral load assays (about 50–200 copies of RNA/ml). Although the goal of any treatment is to restore health and to prolong life, from a practical perspective the

Summary points

Resistance to antiretroviral drugs can emerge quickly (in as short as one week for some drugs)

Once resistance to antiretroviral drugs is established it persists indefinitely

Drug resistance testing is recommended before starting therapy as about 10% of newly infected patients harbour drug resistant variants

Antiretroviral drugs can initially result in paradoxical worsening of some pre-existing conditions ("immune reconstitution syndrome")

The addition of some commonly used drugs to a pre-existing antiretroviral regimen can result in reduced antiretroviral drug levels, leading to suboptimal drug exposures and virological failure

Interruption of antiretroviral therapy is commonly associated with rapid declines in CD4 T cell counts, an increased risk of short term complications, and increased risk of developing drug resistant variants

All nucleoside and nucleotide analogues can cause lactic acidosis or severe hepatic steatosis

Most nucleoside reverse transcriptase inhibitors may need to be dose adjusted in patients with impaired renal function

All non-nucleoside reverse transcriptase inhibitors and protease inhibitors need to be used with care in patients with significant hepatic disease

goal of antiretroviral treatment is to achieve and maintain undetectable plasma levels of HIV RNA. This goal determines almost all of the critical decisions.

When to start therapy

Perhaps the single most important question facing a treatment naive patient is when to start antiretroviral therapy. Ideally such a decision would be informed by

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a randomised clinical study comparing immediate treatment with deferred treatment. No such study has ever been done nor is it likely to be feasible.

Data from several well carried out prospective observational studies have consistently shown that the pretreatment CD4 T cell count rather than the plasma HIV RNA level is the single best predictor of morbidity and mortality in patients starting therapy. These same studies have shown that deferring therapy until CD4 T cell counts are less than $200 \times 10^6/l$ is associated with increased risk of progressing to AIDS or death, compared with starting therapy with a CD4 T cell count above this threshold.^{2 3}

The clinical benefit of starting therapy at higher CD4 T cell counts has not been established. From a pathogenesis perspective, however, untreated HIV infection is associated over time with many untoward effects, including an increased risk for serious complications such as lymphoma and perhaps tuberculosis; a progressive and probably irreversible loss of immunological function; an increasing diversity of the HIV quasi-species, which may be associated with the de novo emergence of drug resistance mutations; increased risk for the development of potentially more virulent viruses; and progressive loss of neurological function. HIV is a virulent virus that causes clear if not dramatic harm throughout its course.

Box 1 Nucleoside and nucleotide reverse transcriptase inhibitors

Abacavir

Associated with potentially life threatening hypersensitivity reactions in about 5% of people

Didanosine (ddI)

Must be given in fasting state

Associated with peripheral neuropathy and pancreatitis

Avoid or use with caution in regimens containing tenofovir

Emtricitabine (FTC)

Similar characteristics as lamivudine

May be associated with reversible skin pigmentation

Generally used as coformulation with tenofovir

Lamivudine (3TC)

Cornerstone of most first line regimens owing to its well established safety and potency

Often used in "salvage" because resistance to this drug enhances activity of zidovudine, stavudine, and tenofovir, and because resistance mutations reduce fitness

Tenofovir

Popular first line drug owing to its well established tolerability and potency

May cause renal dysfunction when used in combination with other potentially nephrotoxic drugs or in patients with other risk factors for renal disease

Stavudine (d4T)

Associated with development of lipodystrophy

Other toxicities include peripheral neuropathy, pancreatitis, and high risk of lactic acidosis (compared with other nucleotide reverse transcriptase inhibitors)

Zidovudine (ZDV, AZT)

Associated with anaemia and neutropenia, particularly in patients with advanced disease

May cause lipodystrophy

*All nucleoside and nucleotide analogues have been associated with lactic acidosis and hepatic steatosis

Despite these well accepted risks of untreated HIV infection, current guidelines generally do not recommend early intervention, in part because the toxicity associated with antiretroviral drugs may be greater than the risks of HIV replication. As discussed in detail below, antiretroviral therapy can be associated with a variety of short term and long term toxicities, including potentially disfiguring redistributions of body fat (lipodystrophy). Also, the ongoing requirement for strict adherence to a daily treatment regimen can negatively affect quality of life, at least for some.

Given the lack of clarity about the risks and benefits of starting therapy in patients with CD4 T cell counts greater than $200 \times 10^6/l$, most guidelines are conservative and generally suggest that patients only consider therapy.⁴⁻⁶ However, as the safety and tolerability of first line regimens improve and as the regimens become increasingly convenient, it is expected that future guidelines will recommend treatment earlier and earlier in the clinical course of HIV disease.

Adherence

A critical component in any decision to start therapy is the patient's perceived ability to adhere to drugs indefinitely. Starting therapy in patients who are not fully committed may lead to poor adherence and virological failure. Since resistance is likely to emerge in such patients, it is often better to defer therapy until access and adherence to drugs can be guaranteed.⁴ These same considerations argue for stopping therapy in patients who become non-adherent; however, any decision to stop therapy to prevent emergence of drug resistance must also consider the rapid immunological progression that can occur.⁷

What to start

In contrast to the "when to start" question, the "what to start" question is based on a growing number of rigorous, well carried out randomised clinical studies. Collectively, these studies support the recommendations that a first line regimen should include a "backbone" of two nucleoside reverse transcriptase inhibitors and a third "anchor" drug that can be either a non-nucleoside reverse transcriptase inhibitor or a ritonavir boosted protease inhibitor (boxes 1-3).⁴⁻⁶ Three options are generally recommended for the nucleoside analogue backbone, all available as fixed dose combination pills: once daily tenofovir plus emtricitabine, once daily abacavir plus lamivudine, or twice daily zidovudine plus lamivudine (although the latter may no longer be preferred given the association of zidovudine with lipodystrophy and anaemia).^{8 9}

A growing and impressive database supports the use of efavirenz as the preferred first line anchor drug. Efavirenz is a highly effective and generally well tolerated non-nucleoside reverse transcriptase inhibitor that is taken once daily.¹⁰ Because of a potential for neural tube defects, efavirenz should be used with caution in women of childbearing age. Also, efavirenz causes short term side effects of the central nervous system and should be used with caution in patients with severe psychiatric illnesses or active substance misuse. Nevirapine is a reasonable alternative for efavirenz but should not be used in women with a CD4 T cell count greater than $250 \times 10^6/l$ or in men with a CD4 T cell count greater

than $400 \times 10^6/l$ owing to greatly increased risk of severe hepatotoxicity at higher CD4 T cell counts.

Protease inhibitors may also be used as the anchor drug. Ten protease inhibitors are currently widely available (box 3). Most are rapidly metabolised by the cytochrome *P-450* metabolic system. As ritonavir is a potent inhibitor of cytochrome *P-450 CYP3A* it is often co-administered with other protease inhibitors. The ritonavir mediated increase in serum half lives of the co-administered protease inhibitor results in both less frequent dosing schedules and improved long term efficacy. On the basis of randomised clinical trials, ritonavir plus lopinavir is currently the preferred option for a first line protease inhibitor.¹¹ However, ritonavir plus atazanavir is often used in clinical practice as it can be given once daily and seems to be well tolerated and effective.

Population specific recommendations

Uncertainty remains about the optimal management of some patient populations, including women (both pregnant and non-pregnant), patients co-infected with hepatitis C or tuberculosis, patients with advanced immunodeficiency, and patients with acute HIV infection. Because drug associated toxicity clearly depends in part on sex, it is reasonable to assume that the optimal management of women may differ from that of men. This is particularly relevant to efavirenz, which should not be used in women who may become pregnant owing to the risk of neural tube defects in the developing fetus. Details of the management of HIV during pregnancy can be found in the latest version of the Public Health Service Task Force recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States (www.aidsinfo.nih.gov). The management of other patient populations can be found at the DHHS guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents (www.hivatis.org) as well as in other published guidelines.^{4 6}

Transmitted drug resistance and its effect on what to start

One of the public health consequences of widespread access to drugs is the increased incidence of transmitted drug resistance mutations. In most regions where treatment is widely available, about 10% of newly infected patients harbour virus that is at least partially resistant to one or more antiretroviral drugs.^{12 13} Since resistance to one drug risks rapid failure of the entire regimen, genotypic resistance testing is recommended before starting therapy. Details on the interpretation and use of resistance testing can be found in published guidelines,^{14 15} reviews,^{16 17} and on the web (www.iasusa.org, <http://hivdb.stanford.edu>).

When to switch therapy

There are at least three major reasons to modify or switch therapy once it has been started: drug toxicity; availability of new agents with improved tolerability, safety, or efficacy; and virological failure. Modifying therapy for the first two reasons is typically straightforward, although clinicians need to realise that even in patients with undetectable HIV RNA levels any pre-existing drug resistant virus will likely persist in

Box 2 Non-nucleoside reverse transcriptase inhibitors

Delavirdine

Associated with rash

Rarely used owing to requirement for three times daily dosing

Efavirenz

Potent and highly effective when used in treatment naive patients (with two nucleoside reverse transcriptase inhibitors)

Associated with central nervous system toxicity that typically resolves by week 4

Teratogenic in humans

Nevirapine

Potent and effective when used in treatment naive patients (with two nucleoside reverse transcriptase inhibitors)

Associated with rash (and potentially Stevens-Johnson syndrome)

Also associated with severe hepatotoxicity in women with CD4 T cells counts greater than $250 \times 10^6/l$ and in men with CD4 T cell counts greater than $400 \times 10^6/l$

cellular or tissue reservoirs indefinitely, and that any new treatment regimen needs to remain effective against such archived viruses.¹⁸ The management of patients with incomplete viral suppression ("virological failure") is complicated and beyond the scope of this review (see bmj.com for more details).^{16 19}

When to stop

Many patients (perhaps the majority) eventually interrupt therapy. Within clinical practice this is often done for one of many reasons, including intolerance to drugs, a desire for a break from taking drugs on a daily basis, a sense of futility (particularly among those with virological failure), a sense that the toxicity of drugs outweighs the benefits, and an inability to access drugs owing to loss of insurance or any means to pay for them.

Intense interest remains in strategies that seek to maintain clinical and immunological health while minimising exposure to expensive and potentially toxic antiretroviral drugs. One common approach is to interrupt therapy once CD4 T cell counts increase to above a predetermined level (for example, $350 \times 10^6/l$) and then resume therapy once cell counts decline to below a lower threshold (for example, $250 \times 10^6/l$). One large international randomised study of continuous compared with CD4 T cell count driven intermittent therapy was stopped early because of an excessive number of clinical events in those interrupting therapy.²⁰ These studies, plus our increasing understanding of HIV pathogenesis, indicate that the risk of interrupting therapy often outweighs the risk of continuing therapy. Any decision to interrupt therapy needs to be made in the context of these studies and should only be considered in those with a strong reason for not remaining on therapy.

How to manage drug toxicities and other adverse events

In contrast to specifics regarding when and how to start and switch drugs, it is imperative that clinicians are aware of the presentation and management of antiretroviral toxicities (see bmj.com for a more detailed discussion).^{21 22}

Abacavir hypersensitivity

Abacavir is a potent nucleoside analogue that is commonly used in one of three formulations. A small proportion (about 5%) of abacavir treated patients develops a hypersensitivity reaction. Most symptoms are non-specific and include fever, nausea, abdominal pain, diarrhoea, malaise, and rash. This reaction typically presents during the first six weeks of treatment but may occur after months of exposure to abacavir. Continued administration of abacavir leads to progressive symptoms that only resolve once the drug

is discontinued. Subsequent re-exposure to abacavir can lead to an immediate life threatening reaction characterised by hypotension and respiratory failure.

Nucleoside analogue associated lactic acidosis

The Food and Drug Administration issued the following warning about all nucleoside reverse transcriptase inhibitors: "lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals." This complication is more common in women and obese people and may be more common with stavudine than with other nucleoside or nucleotide analogues. These drugs should be discontinued in any patient presenting with unexplained lactic acidosis.

Tenofovir associated renal dysfunction

Tenofovir is a potent generally well tolerated and highly effective nucleotide reverse transcriptase inhibitor. Still, most cohort studies indicate that tenofovir is associated with a consistent but mild decrease in the estimated glomerular filtration rate.⁹ Current guidelines recommend that tenofovir should be dose adjusted or not used in patients with renal impairment.

Nevirapine associated hepatotoxicity

Nevirapine may cause a rash during the first few weeks of dosing. This rash can be severe and life threatening. Nevirapine is also associated with increased risk of drug associated hepatitis (about 1% to 2% of patients in one study had grade 3 or 4 increase in transaminases).²³ For reasons that are unclear the risk of severe hepatotoxicity is higher in patients with higher CD4 T cell counts.

Lipodystrophy and abnormal fat redistribution syndromes

HIV associated lipodystrophy generally refers to a vaguely defined syndrome that may include fat redistribution (lipoatrophy or central fat accumulation, or both); hyperlipidaemia; and insulin resistance or diabetes mellitus. These latter metabolic abnormalities are more common in patients receiving protease inhibitors.

Although rarely life threatening, treatment associated redistribution of body fat is probably the single most dominant concern among patients. In the absence of treatment, HIV infection is associated with progressive loss of subcutaneous fat (both peripherally and centrally).²⁴ In the presence of drugs, progressive facial and limb lipoatrophy may occur, resulting in a disfiguring appearance that is unique but difficult to quantify. The use of stavudine and perhaps zidovudine is associated with increased risk of lipoatrophy. Besides surgical correction, the only proved treatment for lipoatrophy is switching from stavudine or zidovudine to another nucleoside reverse transcriptase inhibitor.⁸

Antiretroviral therapy can also cause an abnormal accumulation of body fat. Various unique presentations have been described, including increased abdominal girth (the result of accumulation of visceral rather than subcutaneous fat), breast enlargement, and the appearance of a dorsocervical fat pad ("buffalo hump"). The mechanism for fat accumulation is not known.

Immune reconstitution syndrome

A major proportion of patients starting an effective combination antiretroviral regimen may have a

Box 3 Protease and fusion inhibitors**Atazanavir**

May be administered once daily with or without ritonavir
Popular first line option owing to once daily dosing and to limited effect on lipid levels
May cause elevations in indirect (unconjugated) bilirubin

Darunavir

Must be co-administered with ritonavir
Highly effective for drug resistant HIV
Generally well tolerated

Fosamprenavir

May be administered with or without ritonavir
Associated with gastrointestinal symptoms and rash

Indinavir

May be administered with or without ritonavir
Must be given after fasting every eight hours unless co-administered with ritonavir
May cause kidney stones

Lopinavir

Only available as a capsule or tablet co-formulated with ritonavir
Preferred first line option owing to robust nature of clinical trial data
Causes gastrointestinal symptoms and lipid abnormalities

Nelfinavir

Can not be administered with ritonavir
Less effective than ritonavir boosted protease inhibitor options
Causes diarrhoea

Ritonavir

Rarely used at antiHIV therapeutic doses owing to unfavourable adverse event profile
Potent inhibitor of certain *P-450* isoenzymes and drug transporters
Often used as a pharmacological enhancer to boost exposure of others drugs metabolised by *P-450 CYP3A*
All ritonavir based regimens cause hyperlipidaemia, gastrointestinal distress, and perhaps insulin resistance

Saquinavir

Soft gel formulation recently taken off market
Hard gel formulation must be co-administered with ritonavir

Tipranavir

Must be co-administered with ritonavir
Highly effective for drug resistant HIV
Often only used in patients with limited therapeutic options owing to risk for severe hepatotoxicity

Enfuvirtide

Fusion inhibitor
Must be given parenterally
Associated with severe local site reactions
Generally used in patients with highly resistant HIV

paradoxical worsening of a pre-existing condition or may present in the first few weeks of therapy with a new opportunistic infection. This syndrome is believed to be the result of the rapid expansion of antigen specific immune responses in patients with clinical or sub-clinical disease. Immune reconstitution syndrome, or immune reconstitution inflammatory syndrome, is more common in patients who start therapy with a low CD4 T cell count ($<50 \times 10^6/l$) and in patients who have a potent virological response to therapy.²⁵

The management of immune reconstitution inflammatory syndrome has not been carefully defined. In addition to aggressive treatment of the presenting condition, options include interrupting therapy or starting anti-inflammatory drugs, or both. Both of these options have potential negative consequences and should be considered only in severe cases.

How to manage drug-drug interactions

An extensive list of potential drug-drug interactions is associated with antiretroviral therapy. Several websites provide continued updates for these drug interactions (for example, the database of antiretroviral drug interactions maintained at www.hivinsite.ucsf.edu). However, HIV experts and non-experts should be aware of the more common and serious interactions.

Ritonavir is a potent *P-450 CYP3A* inhibitor and is often used to "boost" other protease inhibitors. Ritonavir also decreases the metabolism of several other drugs, including the statins, benzodiazepines, and most drugs used for erectile dysfunction. Important and potentially life threatening drug interactions can occur between protease inhibitors and immunosuppressants, antiarrhythmics, and ergot derivatives. Other protease inhibitors may have similar effects on *P-450* and therefore should be used with caution even if given without ritonavir.

The absorption and metabolism of antiretroviral drugs can be altered by other drugs in important ways. For example, the widely used proton pump inhibitors reduce atazanavir levels through unknown mechanisms. Also, rifampin (and to a lesser degree rifabutin) can induce *P-450 CYP3A* thereby resulting in increased metabolism of the non-nucleoside reverse transcriptase inhibitors and some protease inhibitors. In either case, suboptimal exposure to the antiretroviral drug may occur, leading to virological failure and the emergence of drug resistance.

Global perspectives

Combination antiretroviral therapy is now becoming more widely available throughout the world, including resource poor regions such as Africa and South East Asia. The goal of therapy is the same in these regions as they are in more industrialised countries. However, when to start therapy and what to start may vary from region to region, depending on both drug availability and costs.

Given the limited resources available in many areas of the world, it is unlikely that frequent viral load monitoring and resistance testing will be widely available in the near future. It is also unlikely that the drugs necessary to construct complicated, fully suppressive salvage regimens will be limited in many regions. Thus,

although the goal of therapy for treatment naive patients will remain similar, the management of treatment failure will likely vary dramatically between regions. These issues are discussed in detail elsewhere (see www.who.int/hiv/pub/guidelines).

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- Gulick RM, Mellors JW, Havlir D, Eron JJ, Gonzalez C, McMahon D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. *N Engl J Med* 1997;337:734-9.
- Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet* 2002;360:119-29.
- Hogg RS, Yip B, Chan KJ, Wood E, Craib KJ, O'Shaughnessy MV, et al. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *JAMA* 2001;286:2568-77.
- Yeni PG, Hammer SM, Hirsch MS, Saag MS, Schechter M, Carpenter CC, et al. Treatment for adult HIV infection: 2004 recommendations of the International AIDS Society-USA Panel. *JAMA* 2004;292:251-65.
- Panel on clinical practices for treatment of HIV Infection convened by the Department of Health and Human Services (DHHS). Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents, 4 May 2006. www.hivatis.org (accessed 17 May 2006).
- Gazzard B. British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2005). *HIV Med* 2005;6(suppl 2):1-61.
- Lawrence J, Mayers DL, Hullsiek KH, Collins G, Abrams DI, Reisler RB, et al. Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus. *N Engl J Med* 2003;349:837-46.
- Carr A, Workman C, Smith DE, Hoy J, Hudson J, Doong N, et al. Abacavir substitution for nucleoside analogs in patients with HIV lipodystrophy: a randomized trial. *JAMA* 2002;288:207-15.
- Gallant JE, DeJesus E, Arribas JR, Pozniak AL, Gazzard B, Campo RE, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med* 2006;354:251-60.
- Staszewski S, Morales-Ramirez J, Tashima KT, Rachlis A, Skiest D, Stanford J, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med* 1999;341:1865-73.
- Walmsley S, Bernstein B, King M, Arribas J, Beall G, Ruane P, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med* 2002;346:2039-46.
- UK Group of Transmitted HIV Drug Resistance. Time trends in primary resistance to HIV drugs in the United Kingdom: multicentre observational study. *BMJ* 2005;331:1368-71.
- Wensing AM, van de Vijver DA, Angarano G, Asjo B, Balotta C, Boeri E, et al. Prevalence of drug-resistant HIV-1 variants in untreated individuals in Europe: implications for clinical management. *J Infect Dis* 2005;192:958-66.
- Hirsch MS, Brun-Vezinet F, Clotet B, Conway B, Kuritzkes DR, D'Aquila RT, et al. Antiretroviral drug resistance testing in adults infected with human immunodeficiency virus type 1: 2003 recommendations of an International AIDS Society-USA Panel. *Clin Infect Dis* 2003;37:113-28.
- Vandamme AM, Sonnerborg A, Ait-Khaled M, Albert J, Asjo B, Bacheler L, et al. Updated European recommendations for the clinical use of HIV drug resistance testing. *Antivir Ther* 2004;9:829-48.
- Clavel F, Hance AJ. HIV drug resistance. *N Engl J Med* 2004;350:1023-35.
- Johnson VA, Brun-Vezinet F, Clotet B, Conway B, Kuritzkes DR, Pillay D, et al. Update of the drug resistance mutations in HIV-1: Fall 2005. *Top HIV Med* 2005;13:125-31.
- Opravil M, Hirschel B, Lazzarin A, Furrer H, Chave JP, Yerly S, et al. A randomized trial of simplified maintenance therapy with abacavir, lamivudine, and zidovudine in human immunodeficiency virus infection. *J Infect Dis* 2002;185:1251-60.
- Deeks SG. Treatment of antiretroviral-drug-resistant HIV-1 infection. *Lancet* 2003;362:2002-11.
- Episodic CD4 guided use of antiretroviral therapy is inferior to continuous therapy: Results of the SMART study. Program and abstracts of the 13th conference on retroviruses and opportunistic infections, 5-8 Feb. Denver, CO; 2006.
- Schambelan M, Benson CA, Carr A, Currier JS, Dube MP, Gerber JG, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA panel. *J Acquir Immune Defic Syndr* 2002;31:257-75.
- Carr A, Cooper DA. Adverse effects of antiretroviral therapy. *Lancet* 2000;356:1423-30.
- Van Leth F, Phanuphak P, Ruxrungtham K, Baraldi E, Miller S, Gazzard B, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet* 2004;363:1253-63.
- Bacchetti P, Gripshover B, Grunfeld C, Heymsfield S, McCreath H, Osmond D, et al. Fat distribution in men with HIV infection. *J Acquir Immune Defic Syndr* 2005;40:121-31.
- French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. *AIDS* 2004;18:1615-27.

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