

Anesthetic Considerations in Non-AIDS HIV-Positive Patients

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Amid the proliferation of literature about acquired immunodeficiency syndrome (AIDS) patients, few authors have looked at the specific problem of anesthetic considerations in patients infected by the human immunodeficiency virus (HIV) who have not developed AIDS. Globally, the AIDS epidemic has spread quickly; since 1997, however, the opposite is true in large industrialized countries where the availability of effective antiretroviral treatments has led to a sharp drop in AIDS cases. Nevertheless, while the prevalence of AIDS is down, cases of HIV continue to rise. Although these seropositive patients are not as ill as they would be with AIDS, they remain a group that requires special anesthetic considerations because an HIV infection can be symptomatic in a patient without the development of opportunistic infections. Moreover, it is essential to understand the perioperative management of antiretroviral therapy, the side-effects, and drug interactions with anesthetic agents. Finally, the role of the anesthesiologist in caring for seropositive pregnant women creates an obligation to become familiar with the principles involved.

BACKGROUND

Since 1981, when the first 5 reported cases of AIDS were described, we have witnessed the emergence of an illness that, until very recently, was the leading cause of death among 25- to 44-year-olds in the United States. It took Dr. Luc Montaignier 2 years to identify HIV as the agent responsible for AIDS and the first screening test was only developed in 1985. Until the introduction of zidovudine (AZT), the first nucleoside reverse transcriptase inhibitor (NRTI) in 1987, the medical profession was powerless in contending with the rising death toll. Despite the development of other NRTIs, it was the marketing launch of saquinavir, the first protease inhibitor (PI) and its association with NRTIs that led to the first significant reduction in AIDS mortality.

Demographic trends

While developed countries have benefited from these recent advances, the same is not true of third world countries where, for cultural and economic reasons, the AIDS epidemic is reaching alarming proportions. The most affected regions include sub-Saharan Africa where an estimated 7.5% to 8.5% of the adult population is infected by HIV, with the figure rising to 30% in parts of Central Africa. The rate is also climbing very rapidly in India and southeast Asia which, to date, have been less affected than sub-Saharan Africa and the Caribbean. In most of these regions, the spread of the virus is most commonly through heterosexual transmission.

In North America, there has been a substantial decline in new AIDS cases and related deaths since 1995. Unfortunately, in contrast, the prevalence of HIV continues to rise. This disparity is the result of the effective treatments now available and their early use. Presently, although bisexual and homosexual males, refugees from endemic countries, and intravenous drug users are the most widely affected groups, the fastest growing group with HIV is women of childbearing age.

THE HUMAN IMMUNODEFICIENCY VIRUS (HIV)

HIV is a retrovirus in the lentivirus subgroup with a particular tropism for CD₄ T-lymphocytes, and monocytes as well as their derivative cells (eg, macrophages, microglia). HIV has been isolated in all biological fluids ranging from blood to mother's milk and infects a new organism when one of these fluids comes into contact with injured mucus membranes or directly with the vascular bed.

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Natural history

After inoculation, the virus can be grown in plasma in as little as 5 days. Two to 8 weeks after infection, up to 80% of patients display non-specific transitory symptoms similar to mononucleosis (fever, fatigue, adenopathy, myalgia, pharyngitis etc.). This viral syndrome is associated with a sharp decline in CD₄+ T-lymphocytes (CD₄) and an increased viral load (VL), both of which are transitory (Figure 1). The syndrome is followed by a period of 10 to 12 years, during which the VL climbs, while the CD₄ level gradually declines to 200/mm³, a level closely associated with the development of AIDS. Although 85% of untreated infected patients follow this pattern, for 10%, the development phase is as short as 2 to 3 years and the remaining 5% never go on to develop AIDS. Since the infectious risk is associated with VL, the two most dangerous periods are the primary infection and AIDS.

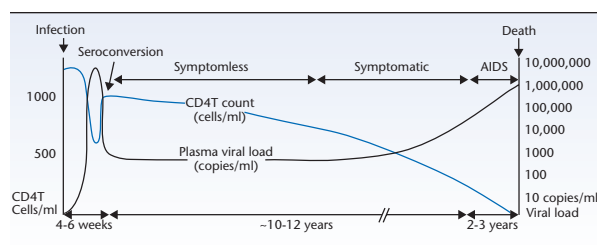
Clinical signs

In 1993, the U.S. Center for Disease Control (CDC) introduced a classification system based on patient symptomatology and CD₄ count (Table 1). Any patient with an opportunistic infection or a CD₄ count <200/mm³ was defined as having AIDS. In practice, the two are highly correlated. Although they do not develop AIDS in the strict sense, patients at clinical stage B are symptomatic by definition. The manifestations of particular interest to anesthesiologists are thrombocytopenia and peripheral neuropathy.

Thrombocytopenia is directly related to the CD₄ count.¹ Only 3% of patients with a CD₄ count >400/mm³ are thrombocytopenic (<150 G/L), whereas the rate rises to 10% with CD₄ counts <400/mm³. In rare cases, thrombocytopenia is even more serious with a platelet count <50 G/L. This thrombocytopenia generally responds to antiretroviral administration. If a faster response is required or, more infrequently, if treatment proves ineffective, these patients usually respond to the same therapy as cases of idiopathic thrombocytopenic purpura, eg, the administration of glyocorticoids and intravenous immunoglobulins.

Similarly, the prevalence of peripheral neuropathy increases as the immune system of the HIV-infected patient deteriorates.² While 2% of patients with CD₄ counts >500/mm³ develop symptoms, the rate rises to 30% among AIDS patients. Moreover, histopathological studies of the latter found characteristic anomalies in nearly 100% of specimens examined. Several forms of peripheral neuropathy have been identified in HIV-infected patients. The most common, distal sensory neuropathy, is a painful syndrome that primarily attacks the feet. To complicate diagnosis, a similar syndrome can occur with the use of NRTIs, particularly didanosine, zalcitabine, and stavudine. In both cases, lower doses of NRTIs or their replacement with another type of antiretroviral agent is usually the first therapeutic manoeuvre. Of particular interest to anesthesiologists, cardiac autonomic dysfunction is found in nearly 15% of patients, regardless of their stage. Although the prevalence of the neuropathies mentioned above increases with the decline in CD₄ count,

FIGURE 1: Evolution of HIV/AIDS



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an HIV-infected patient can develop *mononeuritis multiplex* (a simultaneous or sequential attack on numerous anatomically noncontiguous nerves) at any time. More rarely, Guillain-Barré syndrome can develop, especially during the asymptomatic phase.

VL is another prognostic factor alongside CD₄ count. While CD₄ count yields a clearer picture of a patient's existing immunological condition, VL provides an indication of the disease progress.

ANTIRETROVIRAL THERAPY

As a general rule, all symptomatic (stage B) or AIDS (stage C) patients benefit from antiretroviral therapy. The decision to treat an asymptomatic (stage A) patient is more complex and requires a consideration of CD₄ count and VL. The special case of pregnant women will be discussed later.

Since 1997, antiretroviral therapy has consisted of a combination of antiretroviral agents, usually two NRTIs and a PI. In 50% to 70% of patients, effective antiretroviral therapy reduces the VL to below the detection threshold (50 copies/mL) within 20 weeks after the start of treatment.

Three classes of molecules are presently used to treat HIV infections : NRTIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs), and PIs (Table 2). Enfuvirtide (marketed in Canada since October 2003) is the first molecule in a new class of antiretrovirals: fusion inhibitors. It is the only treatment currently available for patients who develop multiple resistance to antiretrovirals and costs \$29,000 annually. Although enfuvirtide is only administered subcutaneously and an injectable form of AZT has been developed, all the other antiretrovirals must be taken orally.

TABLE 1: CDC infectious stages (1993 definitions)

	Clinical Stage		
	A Asymptomatic primary infection or chronic diffuse adenopathy	B Symptomatic infection (excluding A and C)	C AIDS
Lymphocyte CD ₄ count (cells/mm ³)			
≥ 500	A1	B1	C1
200-499	A2	B2	C2
< 200	A3*	B3*	C3*

* By definition, any patient with CD₄ <200/mm³ is considered to have developed AIDS.

TABLE 2: List of antiretrovirals available in Canada

Nucleoside reverse transcriptase inhibitors (NRTI)	Non-nucleoside reverse transcriptase inhibitors (NNRTI)	Protease inhibitors (PI)	Fusion inhibitors
Abacavir (ABC, Ziagen™)	Delavirdine (Rescriptor™)	Amprénavir (Agenerase™)	Enfuvirtide (Fuzeon™)
Didanosine (DDI, Videx™, Videx EC™)	Éfavirenz (Sustiva™)	Atazanavir (Reyataz™)	
Lamivudine (3TC, Epivir™)	Nevirapine (Viramune™)	Indinavir (Crixivan™)	
Stavudine (D4T, Zerit™)		Lopinavir / Ritonavir (Kaletra™)	
Zalcitabine (DDC, Hivid™)		Nelfinavir (Viracept™)	
Zidovudine (AZT, Retrovir™)		Ritonavir (Norvir™)	
Lamivudine/Zidovudine (Combivir™)		Saquinavir (Fortovase™, Invirase™)	
Abacavir/Lamivudine/Zidovudine Trizivir™)		Tenofovir (Viread™)	

Nucleoside reverse transcriptase inhibitors (NRTIs)

NRTIs were the first molecules developed. By taking the place of amino acids, NRTIs interfere with the synthesis of new viral DNA during reverse transcription by becoming the chain terminator. Despite their superior affinity for reverse transcriptase, NRTIs also antagonize human polymerase DNA activity that gives rise to multiple toxicity. Aside from the peripheral neuropathy discussed earlier, two other NRTI-related toxicities warrant a closer look: lactic acidosis and anemia.

The result of mitochondrial respiratory chain toxicity, lactic acidosis is now recognized as a frequent complication of NRTI therapy. From 8% to 18% of patients have lactate levels >2 mmol/L and the rate rises to 35% among children.³ More disturbing, 92% of a group of 38 newborns exposed to an NRTI *in utero* and AZT during the first 6 weeks after birth had high lactate levels that, in some cases, lasted up to 6 months.⁴ Three syndromes have been described: subclinical hyperlactatemia, symptomatic hyperlactatemia, and lactic acidosis. Encompassing nearly all patients with high lactate levels, subclinical hyperlactatemia involves an asymptomatic increase in lactate levels to between 2.0 and 5.0 mmol/L. The prognosis is excellent and requires no therapeutic adjustment. In addition to the increase in lactate, for each year of exposure to NRTIs, nearly 1% of patients develop nausea, abdominal pain, and weight loss. This symptomatic hyperlactatemia calls for an immediate halt to NRTI treatment. Finally, lactic acidosis is a rare phenomenon associated with a >50% mortality rate and distinguished by lactate levels >5 mmol/L, a pH<7.3, and a fatty liver.

Although chronic HIV infection causes anemia, the use of NRTIs, especially zidovudine, has also been closely related to decreased hemoglobin levels. However, new studies tend to attribute most of the medullary toxicity to chronic HIV infection. In fact, although nearly one-third of HIV-infected patients at all stages combined are anemic (hemoglobin <100 g/L), the rate drops to almost 4% in those who have not developed AIDS and it can be attributed to taking NRTIs in only

one-quarter of the latter.⁵ In addition, initiating treatment using a combination of antiretrovirals, with or without zidovudine, usually leads to a rise in hemoglobin levels. Regardless of the mechanism, the use of erythropoietin has proved effective with these patients.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

NNRTIs only became available relatively recently. NNRTIs attack viral DNA synthesis and they inhibit viral reverse transcriptase very specifically. Therefore, they have few side effects, but are highly susceptible to the development of resistance. Since a single amino acid mutation often suffices, NNRTIs should never be used alone. Side effects include a transitory occurrence of maculopapular erythema, often associated with nevirapine. An increase in transaminases is also sometimes found and, in rare cases, patients develop outright hepatitis. The cytochrome P450 inductor effect will be discussed below.

Protease inhibitors (PIs)

A revolutionary treatment for HIV infection, PIs block proteolysis of the polypeptides essential for the formation of infectious viral particles. Like NNRTIs, PIs are particularly susceptible to the emergence of resistance when used alone. They are less well-tolerated by the gastrointestinal system and produce a number of other side effects, including an increase in hepatic enzymes, lipodystrophia, cytochrome P450 inhibition, metabolic anomalies, and cardiac morbidity. Lipodystrophy and cytochrome P450 inhibition will be discussed below. The following section will focus on metabolic anomalies and the rise in cardiac morbidity.

Antiretroviral treatment involving ≥1 PIs disturbs the lipid balance in a patient and is associated with a decrease in HDL cholesterol and an increase in triglycerides. These anomalies appear to resist conventional therapy and substituting another antiretroviral (eg, an NNRTI) is a common strategy. Diabetes is another less well-documented morbidity associated with PI use and is 3 to 4 times more prevalent among patients taking antiretrovirals. A double-blind, placebo-controlled randomized study associated the use of lopinavir and

ritonavir by healthy volunteers with the development of insulin resistance.⁶ Hepatic and adipose proteasomes are also inhibited by taking PIs. A new PI, atazanavir, appears to be more viral protease-specific and has not been associated with cases of diabetes or lipid imbalance.

Several studies have established a relationship between antiretroviral treatment and the risk of myocardial infarction (MI), in some cases actually doubling the risk.⁷ Besides the metabolic problems described above and the aging of the infected population, several authors have attributed an independent effect of PIs to account for some of the cardiac morbidity. While a retrospective study specifically focused on cardiovascular morbidity failed to link it to the use of PIs, 3 other studies, 1 of them prospective, found a connection between the cumulative use of PIs and the risk of MI.

ANESTHETIC CONSIDERATIONS

Type of intervention

Approximately 20% of seropositive patients require an operation in the course of their illness. Excluding AIDS patients, surgery is usually performed for the same indications as in uninfected patients; however, patients treated with ≥ 1 PIs increasingly undergo plastic surgery. In a study of 116 patients treated with ≥ 1 PIs for an average of 13.6 months, up to 64% developed atrophy of peripheral adipose tissue, sometimes associated with abdominal obesity and the formation of a "buffalo hump."⁸ This lipodystrophy is a highly visible stigma of antiretroviral therapy and increasing numbers of patients undergo corrective surgery (eg, liposuction, submalar implants, excision of the "buffalo hump," etc.)

Preoperative assessment

It is essential that all HIV-infected patients facing elective surgery have a recent CD₄ count on file for preoperative assessment by the anesthesiologist. If the patient has a CD₄ count $>500/\text{mm}^3$ and is not taking antiretrovirals, the chances of any HIV-related complication are very slim. However, if the CD₄ count is $<200/\text{mm}^3$, the lower the count, the higher the perioperative mortality rate. There are numerous articles for reference detailing AIDS-related complications.^{9,10}

The anesthesiologist often encounters patients with CD₄ counts in the $200/\text{mm}^3$ to $500/\text{mm}^3$ range who are receiving antiretroviral therapy. The focus for these patients should be to rule-out the possibility of hemorrhagic diathesis, peripheral neuropathy, or ischemic cardiac pathology. If regional anesthesia is planned, a pertinent neurological exam should be on record. In addition to a recent CD₄ and complete blood count, electrolyte, creatinine, hepatic enzyme, and glycemia levels, as well as an electrocardiogram should be available. For major surgery, a baseline lactate level should be obtained. Finally, although still controversial, the risk of postoperative infectious complications appears to be higher and the

systematic use of prophylactic antibiotic therapy is probably warranted.¹¹

Antiretroviral therapy and the perioperative period

Interrupting antiretroviral treatment, even for a brief period under the best virological conditions, can increase the VL of a patient by 1000-fold and return the CD₄ count to pretreatment levels.¹² It is therefore important to adjust the anesthetic procedure in order to minimize the impact on antiretroviral therapy. Unlike most clinical cases, where even partial treatment is often beneficial, partial antiretroviral therapy is associated with the rapid onset of resistance.¹³ This is especially important if antiretrovirals are stopped for surgery involving an extended interruption of intestinal function. Two NNRTIs, nevirapine and efavirenz, have long plasma half-lives and, while other antiretrovirals can be stopped on the eve of surgery, these 2 medications must be withdrawn 2 to 4 days before. In the postoperative period, the intravenous form of zidovudine must not be used while awaiting the return of intestinal transit, given the risk of developing resistance. The use of intravenous zidovudine alone is only indicated in obstetrics.

In brief, while no study points to a definitive approach to antiretroviral therapy in the perioperative period, avoidance of treatment interruption is recommended and, if an interruption is unavoidable, treatment should be stopped and resumed in a single time block with the time kept as short as possible. The only exception is for nevirapine or efavirenz that must be stopped 2 to 4 days before the operation.

GENERAL VS REGIONAL ANESTHESIA

Changes in immune system function have been described following the onset of general anesthesia, beginning as early as within 15 minutes and sometimes lasting as long as 2 weeks afterwards. These changes have no clinical consequences for healthy patients. However, as they include a transitory decrease in CD₄ lymphocytes, the effect of general anesthesia on HIV-infected patients has raised numerous concerns about possible acceleration in the development of AIDS. Nonetheless, numerous studies have proven the safety of general anesthesia, including studies where patients underwent cardiopulmonary bypass heart surgery.¹⁴

Since HIV is a neurotropic virus associated with multiple neurological complications, HIV infection has long been considered a contraindication for regional anesthetic procedures due to the fear of exposing the nervous system to viral particles. Hughes et al were the first to conduct a prospective study of the neurological and immune outcomes of patients who received neuraxial anesthesia. The parturients were monitored for a period of 4 to 6 months and demonstrated no neurological complications or immune system

deterioration that could be attributed to the neuraxial procedure.¹⁵ Peripheral nerve blocks, spinal anesthesia, epidural anesthesia, and blood patches were all covered by this study or one of the several subsequent ones, with the same results. Many studies have found HIV in the cerebrospinal fluid of nearly 100% of newly diagnosed patients, which might explain these reassuring findings.

Although there has been no comparative study of the long-term outcomes of patients in relation to the anesthetic technique used, regional anesthesia is probably the best choice when possible. In fact, regional anesthesia makes it possible to minimize drug interactions (see below), interferes less with antiretroviral therapy and, theoretically, is less immunosuppressive.

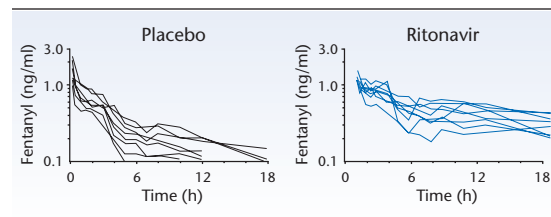
Drug interactions

Despite the proliferation of studies focused on interactions between antiretrovirals and a wide variety of drugs (especially antibiotics), very few have examined the potential interactions with anesthetics. Generally, NNRTIs are cytochrome P450 3A4 inducers, while PIs are inhibitors. A versatile enzyme, cytochrome P450 3A4 has been implicated in the metabolism of opioids (fentanyl, alfentanil, sufentanil, meperidine), benzodiazepines (midazolam, diazepam), and aminoamide local anesthetics (bupivacaine, lidocaine, ropivacaine). Theoretically, NNRTIs should increase the plasma clearance of these substances and therefore, require more frequent administration. Conversely, taking PIs should lead to less frequent administration to achieve the same therapeutic effect. When any of these substances are taken orally, the possibility of a first-pass metabolic increase (or decrease) must be considered in determining the loading dose.

Despite the routine use of these drugs by anesthesiologists, only 3 studies have examined potential interactions with antiretrovirals. The first investigated the effect of ritonavir use on plasma levels of fentanyl following its intravenous administration. In 12 healthy volunteers, the study found a 67% reduction in total clearance (Figure 2).¹⁶ In the second study, the same group found that saquinavir use reduced the total clearance of an intravenous dose of midazolam by 56%, while increasing the maximum plasma concentration (C_{max}) of an oral dose by a factor of 2.3. Finally, the third study reported an increase in the metabolism of oral meperidine with the use of ritonavir. Not only did total clearance rise, but C_{max} dropped by 60%. To explain these findings, the authors suggest that, in addition to being a cytochrome P450 3A4 inhibitor, ritonavir can also be an inducer.

While the use of a single intravenous bolus of anesthetic agents involves little risk, infusions have to be continuously reassessed. Epidural or plexus anesthesia, usually with a continuous infusion combining bupivacaine and fentanyl, must be closely monitored. Given the scarcity of avail-

FIGURE 2: Pharmacokinetics of fentanyl with antiretroviral therapy¹⁶



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able data and the limitations of theoretical models, the use of remifentanyl, oxazepam, and aminoester local anesthetics might be preferable wherever possible. The latter are metabolized by plasma esterase and plasma pseudocholinesterase rather than by cytochrome P450, making the risk of a drug interaction very low, at least theoretically. To avoid any possible interaction, the anesthesiologist can use etomidate, desflurane, and cisatracurium, or other agents not metabolized by cytochrome P450. An up-to-date list of drug interactions with antiretrovirals can be found at <http://hivinsite.ucsf.edu/arvdb?page=ar-00-02>. Accessed: 23/03/2005

Transfusions

Anemia is a common complication of HIV infection, especially with AIDS patients, and blood product transfusions are not rare. Retrospective studies have identified transfusions as a risk factor leading to a higher VL, reactivation of cytomegalovirus (CMV) infections, and higher mortality rates. As a result, some have recommended the use of leukoreduced, irradiated, CMV-negative units. The Viral Activation Transfusion Study, however, found that transfusions had no effect on the immune outcomes of patients.¹⁷

Obstetrics

The World Health Organization has made the reduction of perinatal transmission rates – the prime cause of pediatric HIV infections – a priority, with the aim of cutting it in half by 2010. The perinatal transmission rate is estimated at 15% – 30% (20% – 45% among breastfed newborns), but it could be reduced to < 2% with proper care. Among other factors, perinatal transmission is related to VL; therefore, broader criteria for starting antiretroviral therapy have been proposed. With the exception of efavirenz, a known teratogen, any HIV-infected pregnant woman with a VL >1000 copies/mL should receive the same antiretroviral therapy as patients who are not pregnant. Moreover, even among patients with no prior treatment, prenatal administration of AZT reduced the perinatal transmission rate from 9.8% to 1.0% when the VL was <1000 copies/mL. Therefore, prenatal use of AZT is recommended for these patients. Finally, intravenous administration of AZT is recommended during labour or

before a C-section, and to the newborn for the first 6 weeks after birth, since it reduces the perinatal transmission rate.

Planned C-sections reduce the perinatal transmission rate by 50%, regardless of the use of antiretrovirals. However, this reduction was not found in women already in labour or with ruptured membranes. Moreover, the perinatal transmission rate is already very low among treated patients with a VL <1000 copies/mL. As a result, the American College of Obstetricians and Gynecologists does not recommend elective C-sections for these 3 groups. For more details about caring for HIV-infected pregnant women, see the guidelines published by the National Institutes of Health¹⁸ and available online at <http://aidsinfo.nih.gov/publications/pubresult.asp?Finalpubtype=G>. Accessed: 23/03/2005.

SUMMARY AND CONCLUSIONS

Barring radical changes in lifestyles or the development of an HIV vaccine, anesthesiologists will likely face more and more seropositive patients who have not developed AIDS. To guide the preoperative assessment, a recent CD₄ lymphocyte count between 200 and 500 cells/mm³ should tell the anesthesiologist to look for thrombocytopenia, anemia, or peripheral neuropathy. Patients taking antiretrovirals should be checked for hyperlactatemia, hyperlipidemia, diabetes, or coronary disease. Generally, withdrawing antiretroviral treatment should be avoided but, if necessary, withdrawal should be complete and for as short a time as possible keeping in mind the different half-lives of antiretrovirals. This approach will minimize VL resurgence and the development of resistance. Powerful cytochrome P450 inducers or inhibitors, NNRTIs and PIs affect the metabolism of many anesthetics, especially opiates, benzodiazepines, and the aminoamide local anesthetics. If other agents with a different metabolism cannot be used, the anesthesiologist must administer these drugs with caution, especially when using continuous infusions. Whenever possible, locoregional anesthesia is the procedure of choice for minimizing drug interactions and interference with antiretroviral therapy. Despite initial fears, blood transfusions do not appear to be hazardous. Finally, more liberal use of antiretrovirals with pregnant women has led to a sharp drop in perinatal transmission rates, especially when combined with an elective C-section, unless the patient is already in labour, has ruptured membranes, or a VL <1000 copies/mL.

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