What is HIV Post-exposure Prophylaxis (HIV PEP)?
HIV PEP is a 28-day treatment of antiretroviral drugs taken twice a day to decrease the chance of becoming HIV infected. The HIV PEP drug regimen used by the HIV PEP program is:

- → Combivir® (300 mg zidovudine & 150 mg lamivudine), 1 tablet taken orally twice per day, with or without food; and,
- → Kaletra® (200 mg lopinavir & 50 mg ritonavir), 2 tablets taken orally twice per day, with or without food.

Why does HIV PEP therapy last 28-days?
A 28-day course of HIV PEP therapy to reduce the risk of HIV transmission is recommended by the Centers for Disease Control and Prevention (CDC)[1]. This recommendation is based on evidence from animal studies, which demonstrate that a 28-day course of therapy is more effective at reducing the possibility of HIV infection than a 3-day or 10-day course of HIV PEP medications[2]. Ontario HIV experts fully endorse this recommendation.

Is it beneficial to take the medications for longer than 28-days?
Experts believe that taking HIV PEP for more than 28-days does not provide an additional benefit, therefore it is not recommended.

Are there any benefits to taking HIV PEP for less than 28-days?
Benefits of shorter courses of HIV PEP therapy are unknown. Data from animal studies indicate that even with early initiation of medications (within 24 hours post-exposure), taking a 3-day course of HIV PEP is not effective in preventing HIV, and taking a 10-day course of HIV PEP is only partially effective some of the time. There are many strategies for managing side effects that health care providers can share with clients to support them through the full cycle of medication (or as long as possible).

Why is there a 72-hour post-exposure cut-off for initiation of HIV PEP?
Animal studies have demonstrated incomplete efficacy of HIV PEP when initiated more than 72-hours post-exposure[2,4]. Based on these data, the Centers for Disease Control and Prevention (CDC) recommend that HIV PEP be initiated within 72-hours of exposure to HIV[1].

HIV replicates at an accelerated rate. If the HIV virus has been transmitted, it starts dividing and spreading in the body immediately. If the HIV virus was acquired at the time of the exposure, initiating HIV PEP more than 72-hours after the assault may not aid in halting replication of the HIV virus.

What HIV care is offered to sexual assault victims/survivors presenting more than 72-hours post-assault?

In those cases where the assailant is known to be HIV-positive and penetration has occurred, immediate referral to an HIV expert for further consultation and possible initiation of early HIV treatment for acute HIV infection is recommended. In all other cases where the assailant's HIV status is unknown and penetration has occurred, an immediate HIV test and follow-up HIV testing at 4-6 weeks, 3 and 6 months post-assault is recommended. Most HIV infections will be picked up by the 3-month test.

Why are Combivir® and Kaletra® being used for HIV PEP?

Combivir® and Kaletra® have been chosen as the antiretroviral regimen used by the HIV PEP program for a number of reasons:

- → The regimen is recommended for post-exposure prophylaxis by the Centers for Disease Control and Prevention, Department of Health and Human Services, 2005[1];
- → Minimal number of pills helps to facilitate client adherence, thus reducing the potential for development of a drug-resistant strain of HIV;
- → This combination of antiretroviral drugs is the 'gold standard' of HIV PEP regimens used in Ontario, Canada;
- → The regimen was determined by an ongoing expert advisory panel. In October 2006 the panel met to examine other potential regimens (Result: HIV PEP program shift to new Kaletra® formulation). The panel meets annually to ensure that the HIV PEP regimen remains current, reflecting both individual patient needs as well as organizational needs; and,
- → This regimen was used during the HIV PEP Study. Ontario SATC health care providers are familiar with this regimen and have experience managing side effects and supporting clients taking these medications.

What is the risk of HIV transmission following sexual assault?

Assessing HIV risk is difficult and involves weighing a number of factors, such as assailant and/or assault characteristics.

- → Assaults perpetrated by assailants known to be HIV-positive, or known to be at high-risk of being HIV-positive (e.g., intravenous drug users, a man who has sexual contact with men), increase the risk of HIV transmission.
- → Characteristics of a sexual assault that increase the risk of HIV transmission include the presence of anal, vaginal or oral injuries, the presence of blood in the anus, vagina or mouth, the presence of sexually transmitted infections or ulcerations (open sores) on the genitals, assault by multiple assailants, and/or assault including multiple receptive sites (anus, vagina and/or mouth).
- → It is possible that some characteristics of the assault can decrease HIV risk, such as oral penetration only (no vaginal and no anal penetration), no ejaculation, and/or condom use. However, it is important to note that these factors are often difficult to assess in cases of sexual assault, as victims/survivors may not know if the assailant ejaculated or whether

condoms were used properly or at all. Unless no penetration occurs, condom use and/or no ejaculation only potentially decrease the risk and do not make it zero.

Individual HIV risk varies depending on circumstances of the sexual assault. It is important to weigh each individual client's HIV risk on a case-by-case basis.

What are the risks involved in taking HIV PEP (Combivir® and Kaletra®)?

There are two main risks are associated with taking HIV PEP, both of which happen rarely:

1. The potential for adverse effects to occur; and
2. The potential for a drug-resistant strain of HIV to develop, especially if adherence to the HIV PEP regimen is poor.

Potential for Adverse Effects

The majority of people that take Combivir® and Kaletra® experience some common side effects, such as headaches, nausea, fatigue and/or diarrhea. Typically, side effects are not severe; management with over-the-counter remedies often helps to decrease their impact. Clients taking HIV PEP require ongoing support to help cope with and manage any side effects experienced. While most people who develop side effects are able to carry on with their day to day activities, others feel sicker and may need to take time off from work, school, and other daily activities or responsibilities. Potential for development of more serious side effects exists; however data on occurrence of serious adverse effects reflects long-term use of Combivir® and/or Kaletra® in HIV-positive patients. Serious adverse effects are rare during a 28-day cycle of Combivir® and Kaletra®, but may happen. While taking Combivir® and Kaletra® all clients are followed closely.

Combivir® - Anemia (a decrease in red blood cells carrying oxygen) affects about 2% of long-term patients; Loss of white blood cells affects between 4-8% of long-term patients; Muscle-wasting affects approximately 10% of long-term patients; and, Peripheral neuropathy affects approximately 12% of long-term Combivir® patients.

Kaletra® - pancreatitis (inflammation of the pancreas) is a rare side effect of Kaletra®; hepatitis (liver inflammation) is also a rare side effect, more likely to occur in individuals who already have liver disease.

Potential for Development of a Drug-Resistant Strain of HIV

The HIV PEP regimen used by this program is a simple regimen with minimal pills, which helps facilitate adherence. Although development of anti-retroviral drug resistance is possible in the case of the rare individual who may be incubating the HIV virus and who takes the medications erratically, ongoing follow-up counselling helps to ensure that the medications are taken as prescribed. Use of Kaletra®, one of the most potent anti-HIV drugs available, in combination with Combivir® helps reduce the chances of resistance. In instances where HIV PEP fails to prevent infection, the selection of resistant virus by the antiretroviral drugs is theoretically possible.

How effective is HIV PEP at preventing HIV infection?
Antiretroviral drugs have been proven to be effective in preventing HIV transmission following needle-stick exposures[3]. However, due to different types of exposures and ethical concerns regarding study design and sample sizes, there are no efficacy studies of HIV PEP following non-occupational HIV exposures (such as intravenous drug use, or sexual assault).

Probable efficacy of HIV PEP following sexual assault and other non-occupational exposures is supported by data from occupational exposures, animal studies, and the prevention of mother-to-child transmission. A case-control study of health care workers demonstrated an 81% reduction in the likelihood of HIV infection associated with HIV PEP use[3]. Animal studies support the efficacy of HIV PEP following intravenous, oral, and vaginal exposures and have shown that early initiation of HIV PEP (within 24 hours) is more effective in preventing HIV infection than initiation at 48 or 72 hours post-exposure[2,4]. Mother-to-child transmission studies have demonstrated a ⅔ reduction in HIV infections in babies when a combination of pre- and post-exposure prophylaxis were used[5].

Does HIV PEP interact with other medications?
Yes, Combivir® and Kaletra® potentially interact with other medications. Zidovudine (a component of Combivir®) may affect other medications your client is taking and/or other medications may decrease the effectiveness of zidovudine. Severity of side effects to zidovudine may also increase if several other medications are taken concurrently. Kaletra® interacts with many different drugs by affecting the liver cytochrome P450 drug metabolising enzymes, thus it interacts with other drugs that also use the liver. This may result in loss of efficacy of Kaletra®, and/or altered effects of other medications concurrently taken.

For a full list of drugs that Combivir® and Kaletra® may interact with, refer to Appendix 1D of the HIV PEP program Medical Guidelines, or to the product monographs for each drug (Combivir® is manufactured by GlaxoSmithKline; Kaletra® is manufactured by Abbott).

What drugs are absolutely contraindicated with Kaletra®?
The following is a list of drugs that ***cannot be taken in unison with Kaletra®***. Drugs are listed by drug class – not all drugs within each drug class are contraindicated. Only the drugs that are listed are contraindicated with Kaletra®.

Antiarrhythmics	Flecainide (Tambocor®); Propafenone (Rythmol®) *potential for serious of life-threatening arrhythmias*
Antibiotics	Rifampin (Rifadin®, Rofact®); *risk loss of efficacy of lopinavir/ritonavir due to accelerated metabolism by rifampin*
Antihistamines	Astemizole (Hismanol®); Terfenadine (Seldane®)* *potential for serious of life-threatening arrhythmias*

Benzodiazapines	Midazolam (Versad®); Triazolam (Halcion®) *potential for prolonged sedation and/or respiratory depression*
Ergot Derivatives	Bellergal Spacetabs®; Cafergot; Cafergot PB; Dihydroergotamine (Migranal®); Ergodryl; Ergoloid mesylates (Hydergine®); Ergonovine; Ergotamine; Gravergol; Methylergonovine, Methylergotamine (Methergine®) *potential for ergot toxicity, including peripheral vasospasm and ischemia of the extremities and other tissues*
GI Mortality Agents	Cisapride (Propulsid®)* *potential for serious or life-threatening arrhythmias*
Herbal Products	St. John's Wort (hypericum perforatum) *risk loss of efficacy of lopinavir/ritonavir due to accelerated metabolism by St. John's wort*
Neuroleptics	Pimozide (Orap®) *potential for prolonged sedation and/or respiratory depression*
Statins	Lovastatin (Mevacor®); Simvastatin (Zocor®) *potential for myopathy and rhabdomyolysis*

**Product no longer available in Canada, only available in United States.*

What about antidepressants and antipsychotics, like Celexa®, Effexor®, Paxil® and Zyprexa®? What do the experts recommend?
Certain antidepressants including Celexa®, Effexor® and Paxil® and certain antipsychotics like Zyprexa® are commonly used among the SATC client population. HIV PEP is not absolutely contraindicated if a client is taking one of these medications. However, the antidepressant levels may be increased by Kaletra® so they may have more of an effect. This should be discussed with the client. As long as the client is aware of the potential to experience effects of higher doses of antidepressants and agrees to come for their regular follow-up visits, it is fine to start the HIV PEP medications. If the Sexual Assault Nurse Examiner feels that the client is emotionally unstable and at risk of overdosing, it is recommended to use Combivir® alone.

Is it okay to give the first dose of HIV PEP if there is significant concern about health and/or drug contraindications, and an HIV expert is unavailable for consultation?
If you cannot reach an HIV expert – it is okay to dispense the first dose of Combivir® ONLY. However, you must consult with an HIV expert before the next dose is administered (i.e., within 12 hours of administering the first dose). Ontario HIV experts agree that a single dose of Combivir® will not have any negative impacts, regardless of pre-existing health and/or drug contraindications, and is safe to give immediately to at-risk clients. Following consultation with an HIV expert, Kaletra® (or another Protease Inhibitor) may be introduced.

Are there any cases where Combivir® would be contraindicated?

Combivir® is contraindicated in clients:

- → With a known allergy to one of its components (zidovudine and/or lamivudine);
- → Already on a myelosuppressive or hematosuppressive agent (e.g., transplant medications);
- → With a history of bone marrow insufficiency;
- → With severe anemia; and/or
- → With acute pancreatitis.

Is it okay to give other routine medications post sexual assault, such as antibiotics or emergency contraceptives, in unison with HIV PEP?

Yes, prophylactic medications for other sexually transmitted infections and pregnancy can be taken with HIV PEP (e.g., cefixime for gonorrhoea; azithromycin or doxycycline for Chlamydia; and, Plan B/Ovral® for pregnancy).

Do atiretroviral medications decrease the effectiveness of the birth control pill?

Yes, Kaletra® does decrease the effectiveness of the birth control pill. Advise all clients that are on the birth control pill and taking HIV PEP to use additional forms of protection to prevent pregnancy for the 28-days they are taking Kaletra®, and for up to 2 months after completing Kaletra®.

Is it okay to give HIV PEP during pregnancy?

There are important issues related to HIV and antiretrovirals if a woman is pregnant. Antiretroviral drugs are potentially teratogenic (interference with normal embryonic development; potential for birth defects) in the first trimester of pregnancy and therefore, are often avoided during this period. However, if a woman is at increased risk of HIV transmission, the risk of transmission to the fetus is very high during seroconversion; giving antiretroviral drugs in this scenario is more important than the risk of teratogenesis.

If a client is in the first trimester of pregnancy and at increased HIV risk, offer the first dose of HIV PEP immediately, then consult with a physician and/or HIV expert before dispensing subsequent doses of HIV PEP medications. While HIV PEP medications should be available and offered to all at-risk pregnant sexual assault victims/survivors, the decision to continue taking HIV PEP should be made in consultation with an HIV expert.

Is it okay to breastfeed while taking HIV PEP?

Breastfeeding should be discontinued in all clients taking HIV PEP. If suspicion of HIV infection is high enough to start HIV PEP therapy, then breast-feeding should be discontinued. Clients who choose not to take HIV PEP should be informed that the rate of HIV transmission in breast milk is approximately 1 in 4 in order for them to make informed choices about breastfeeding.[6]

Are there weight-adjusted dosing guidelines for adults < 50 kg taking HIV PEP?

No, adults weighing less than 50 kilograms take the regular adult dose:

- → Combivir® (300 mg zidovudine & 150 mg lamivudine) twice per day, and
- → Kaletra® (200 mg lopinavir & 50 mg ritonavir) twice per day

Paediatric weight-based guidelines take into account differences in maturity of gut functioning and enzyme metabolism, which is why dosages are adjusted for paediatric clients < 12 years and < 50 kg in weight. Adjustments are not necessary for adults < 50 kg in weight.

How should Combivir® and Kaletra® be stored after dispensed to clients?

Combivir® and Kaletra® can be stored at room temperature (20°- 25°C). But, they must be stored in a dry place. Advise clients not to store these drugs in their bathroom due to moisture in the air and frequent changes in room temperature. Also, advise clients not to expose these drugs to freezing temperatures (e.g., during travel); if tablets freeze then thaw, the accumulating moisture may compromise the integrity of the tablets. If clients are going to travel with HIV PEP, advise that they bring their medications onboard with them as carry-on.

Does Kaletra® need to be refrigerated?

No, the HIV PEP program is using a NEW formulation of Kaletra® that does require refrigeration at any time (including no refrigeration during storage).

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[1] CDC. 2005. Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Non-occupational Exposure to HIV in the United States: Recommendations from the U.S. Department of Health and Human Services. *MMWR.* 54(RR-2): 1-20.

[2] Tsai CC, Emau P, Follis KE, Beck TW, Benveniste RE, Bischofeberger N, Lifson JD, Morton WR. 1998. Effectiveness of postinoculation (R)-9-(2-phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus SIVmne infection depends critically on timing of initiation and duration of treatment. *Journal of Virology*. 72: 4265–73.

[3] Cardo DM, Culver DH, Ciesielski CA, Srivastava PU, Marcus R, Abiteboul D, Heptonstall J, Ippolito G, Lot F, McKibben PS, Bell DM. 1997. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. *New England Journal of Medicine.* 337(21): 1485-90.

[4] Otten RA, Smith DK, Adams DR, Pullium JK, Jackson E, Kim CN, Jaffe H, Janssen R, Butera S, Folks TM. 2000. Efficacy of postexposure prophylaxis after intravaginal exposure of pig-tailed macaques to a human-derived retrovirus (human immunodeficiency virus type 2). *Journal of Virology.* 74: 9771–5.

[5] Connor EM, Sperling RS, Gelber R. 1994. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *New England Journal of Medicine.* 331(18):1173-1180.

[6] Van de Perre P. 1995. Postnatal transmission of human immunodeficiency virus type 1: the breastfeeding dilemma. *American Journal of Obstetrics and Gynecology*. Vol. 173: 483-487.