

Street/Party Drugs and HAART : How does it work and what must we do



APRIL 2007

**WORKSHOP ON THE
INTERACTIONS BETWEEN
STREET/PARTY DRUGS AND
ANTIRETROVIRAL THERAPY
(and other medications...)**

Jean Clermont-Drolet, RN
Street Nurse, MIELS-Québec

PRESENTATION

- Few Points
- Depressants
- Stimulants
- Hallucinogens

Polyconsumption

Very often, a person uses more than one product. Frequently combined drugs include :

- Alcohol, Tobacco and Cannabis
- Depressants and Alcohol
- Cocaine, Sedatives and Heroin
- Amphetamines, GHB and Ketamine

Toxicity

- Quantity
- Health situation
- Drug-use ways
- **Purity : ? and %**

Immune System

- Capacity decreased or suppressed by most of the drugs, making the body vulnerable to all kinds of infections and diseases.

Enzyme CYP3A4

- **Cytochrome P450 3A4** (abbreviated **CYP3A4**) (EC 1.14.14.1), a member of the cytochrome P450 mixed-function oxidase system, is one of the most important enzymes involved in the metabolism of xenobiotics in the body.
- CYP3A4 is involved in the oxidation of the largest range of substrates of all the CYPs.
- CYP3A4 is also, correspondingly, present in the largest quantity of all the CYPs in the liver.

• Selected inducers, inhibitors and substrates of CYP3A4

Type Agent

INDUCERS : barbiturates (phenobarbital etc), carbamazepine, dexamethasone, hyperforin (constituent of St Johns Wort), non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine, etc), griseofulvin, phenytoin, rifampicin

INHIBITORS : amiodarone, azole antifungals (ketoconazole etc), bergamottin (constituent of grapefruit juice), cimetidine, ciprofloxacin, ciclosporin, diltiazem, imatinib, macrolide antibiotics (erythromycin etc), metronidazole, non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine etc), protease inhibitors (saquinavir etc), selective serotonin reuptake inhibitors (fluoxetine etc), verapamil

SUBSTRATES : amiodarone, azole antifungals (ketoconazole etc), barbiturates (phenobarbital etc), benzodiazepines (diazepam etc), bupirone, calcium channel blockers (diltiazem, nifedipine etc), carbamazepine, codeine, ciclosporin, dextromethorphan, digoxin, ergot alkaloids, ethinylestradiol, fentanyl, haloperidol, HMG-CoA reductase inhibitors (atorvastatin etc), ivabradine, levonorgestrel, lidocaine, macrolide antibiotics (erythromycin etc), mifepristone, estradiol, ondansetron, omeprazole, paracetamol, PDE5 inhibitors (sildenafil etc), quinidine, quinine, selective serotonin reuptake inhibitors (fluoxetine etc), taxanes (paclitaxel etc), testosterone, theophylline, tricyclic antidepressants (amitriptyline etc), valproate, venlafaxine, warfarin, *various anticancer agents*

Notes: Where classes of agents are listed, there may be exceptions within the class.

Non-nucleoside reverse transcriptase inhibitors have been shown to both induce and

Inhibit CYP3A4

Depressants



Depressants

All of these drugs relax the Central Nervous System

- Alcohol
- Tranquilizers (Barbiturates, Benzodiazepines...)
- Narcotics (Opium, Heroin, Codeine, Morphine, Meperidine, Methadone, etc.)
- GHB, Rohypnol

Alcohol + IPs and/or NNRTIs

- Heavy ingestion of alcohol leads to enzyme (CYP2E1 and CYP3A4) inhibition = overtherapeutic level of PIs and NNRTIs.

But

- Chronic ingestion also leads to enzyme induction, which may result in sub-therapeutic levels of PIs and NNRTIs.

Source : www.numedx.com

Alcohol + ABC (NRTI)

- Alcohol increases Abacavir (Ziagen) levels in blood (up to 41% in one study) because ABC is metabolized by alcohol dehydrogenase.

(JA McDoweel, Pharmacokinetic interaction of abacavir and ethanol in immunodeficiency virus-infected adults, Antimicrob Agents Chemother 2000; 44, 1686-1690)

Source : www.numedx.com

Alcohol + ddI (Videx) (NRTI)

- Increased risk of pancreatitis

Source : *Recreational Drugs and HIV Antiretroviral : a Guide to interactions for clinicians*, by NY/NJ AIDS Education and Training Center, Summer 2005

Heroin



Heroin + RTV (PI)

- Ritonavir (Norvir) decreases Heroin levels by 50%, quickly transformed in morphin in blood
- Watch for opiate withdrawal, but caution is in order : RTV and the other PIs have sometimes been known to have opposite effects (they cut methadone levels in real life, while test tube experiments predicted they would increase them).

Source : Anti-HIV Meds + Street Drugs: Some Cocktails Don't Mix

[Notes from the Underground, PWA Health Newsletter Winter 1998-99.](#)

From : http://www.thebody.com/pwa/NFUwin98-99/street_drugs.html

Methadone



Methadone + HIV Infection

- With its mechanisms of metabolization, Methadone can favor infection by HIV by activating the virus and decreasing the production of CD4.

Source : www.harmreduction.org

Methadone + ARV

- Many studies performed.
- FDA made various recommendations depending on which ARV is used simultaneously with methadone.

www.harmreduction.org

Methadone + RTV (PI)

- Ritonavir (Norvir) decreases methadone levels by 40% in blood : Increase in dose of methadone may be considered, according to FDA label.

Source : www.norvir.com

BUT

- Effect unpredictable : either increase or decrease methadone levels.
- Source : **Risky Cocktails : Interactions Between Street Drugs and HIV Medications**, by Guy Pujol.

Source : www.thebody.com/asp/apr03/risky_cocktails.html

Methadone + LPV-RTV (PI)

- Lopinavir-Ritonavir (Kaletra) decreases methadone levels by 53% in blood.
- Dose of methadone may need to be increased, according to FDA label.

Source : www.kaletra.com

Methadone + AZT (NRTI)

- Methadone increases by 50% Zidovudine (Retrovir) levels in blood.
- Dose reduction of AZT not recommended routinely

Source : www.retrovir.com

Methadone + DDI (NRTI)

- Methadone decreases Didanosine (Videx) levels by 52% in blood.
- No recommendations on doses on FDA label.

Source : www.videxec.com

Methadone + EFV (NNRTI)

- Effavirez (Sustiva) decreases methadone levels by 60% in blood.
- Patients taking methadone and EFV may exhibit signs of narcotic withdrawal.
- Methadone dose should be adjusted upward by 5mg to 50 mg, accordingly as written on FDA label.

Source : www.sustiva.com

Methadone + NVP (NNRTI)

- Nevirapine (Viramune) decreases methadone levels by 60% in blood.
- Patients taking methadone and NVP may exhibit signs of narcotic withdrawal.
- Methadone dose should be adjusted accordingly (upward) as noted on FDA label.

Source : www.viramune.com

Methadone + Diflucan

- **Diflucan** (fluconazole) can raise methadone levels in the blood by up to 35%.
- No symptoms of overdose were reported in a 13 people study.

Methadone + Cipro

- **Cipro** (ciprofloxacin), an oral antibiotic used to treat MAC, bacterial pneumonia and many common infections, can cause significant increases in methadone levels.
- This increase could possibly lead to serious sedation and even overdose for some people.

Barbiturates



Barbiturates

Seconal® (Secobarbital)

Nembutal® (Pentobarbital)

Amytal® (Amobarbital)

Tuinal® (Amobarbital-secobarbital)

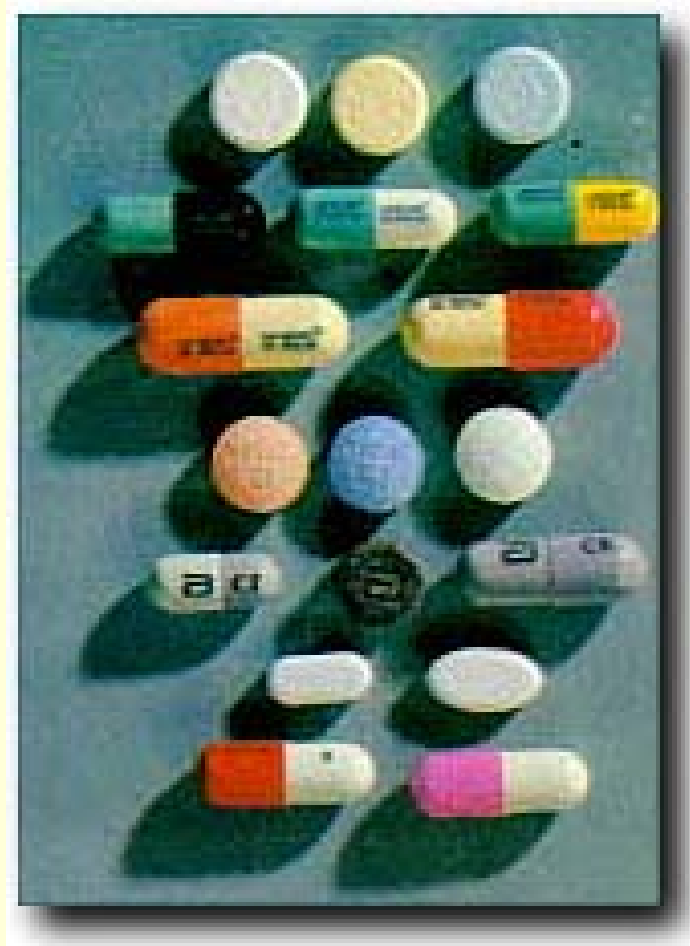
Mandrax® (Methaqualone)

Barbiturates + ARV

- PIs increase blood levels of barbiturates;
- Barbiturates can lower levels of PIs and NNRTIs. This interaction can reduce or eliminate the benefit of the anti-HIV drug, and possibly cause HIV to develop resistance to the drug.

Source : www.numedx.com

Benzodiazepines



Benzodiazepines

Generic Name (®) Average Half-Life

- **Alprazolam** (Xanax) 12-19h
- **Bromazepam** (Lectopam) 10-20h
- **Chlordiazepoxide** (Librium) 6-30h
- **Clonazepam** (Rivotril) 16-20h
- **Diazepam** (Valium) 20-80h
- **Flunitrazepam** (Rohypnol) 15-20h
- **Lorazepam** (Ativan) 10-20h
- **Nitrazepam** (Mogadon) 30-60h
- **Oxazepam** (Serax) 5-10h
- **Temazepam** (Restoril) 3-25h
- **Triazolam** (Halcion) 2-5h

Sedatives + PIs

- PIs inhibit metabolism of sedatives, and increase plasma concentration of Benzodiazepines and/or Barbiturates.
- Use of PIs with Benzo should be avoided due to increased risk of sedation and respiratory depression.
- **Triazolam** (Halcion) and **Midazolam** (Versed) specifically contraindicated with all PIs. It can lead to a very dangerous, even deadly interaction, raising Halcion or Versed levels so much that serious sedation could result, possibly stopping breathing.
- Source : www.numedx.com

Benzodiazepines + RTV (PI)

- Huge increase in blood levels of **Diazepam** (Valium) by **Ritonavir** (Norvir).
- **Temazepam** (Restoril) metabolizes more quickly with **Ritonavir** (Norvir).
- Ritonavir (Norvir) decreases therapeutic effect of **Lorazepam** (Ativan), **Oxazepam** (Serax) and **Temazepam** (Restoril).

Source : www.numedx.com

Benzodiazepines + Delavirdine (NNRTI's)

- Delavirdine (Rescriptor) likely inhibits benzodiazepines metabolism through CYP3A4 inhibition and increases risk of adverse effects : concomittant use should be avoided.

Source : *Recreational Drugs and HIV Antiretroviral : a Guide to interactions for clinicians,*
by NY/NJ AIDS Eduction and Training Center,
Summer 2005

Rohypnol



Flunitrazepam + RTV (PI)

- Ritonavir (Norvir) increases by 2X to 3X the blood levels of Flunitrazepam (Rohypnol).

Source : www.numedx.com

GHB



GHB + PIs

- PIs increase by 5X to 10X the blood levels of GHB : Serious risks of myoclonic or seizure activity, bradycardia, respiratory depression or loss of consciousness.

(Harrington RD, Life-Threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and GHB, Arch. Intern. Med., 1999; 159; 2221-2224)

Source : www.numedx.com

Stimulants



Stimulants

Tobacco

Coffee, Tea

Cocaine

Crack

Amphetamines

Ecstasy

Cocaine



Crack



Cocaine + HIV

- Cocaine could stimulate the viral replication of HIV by 200X as observed in mice, probably because cocaine would increase the number of CCR5 and CXCR4 receptors on CD4 cells (receptors that HIV uses to infect the cells).
- Increases rate of HIV viral replication in vitro.
- No known interactions between Cocaine and ARVs.

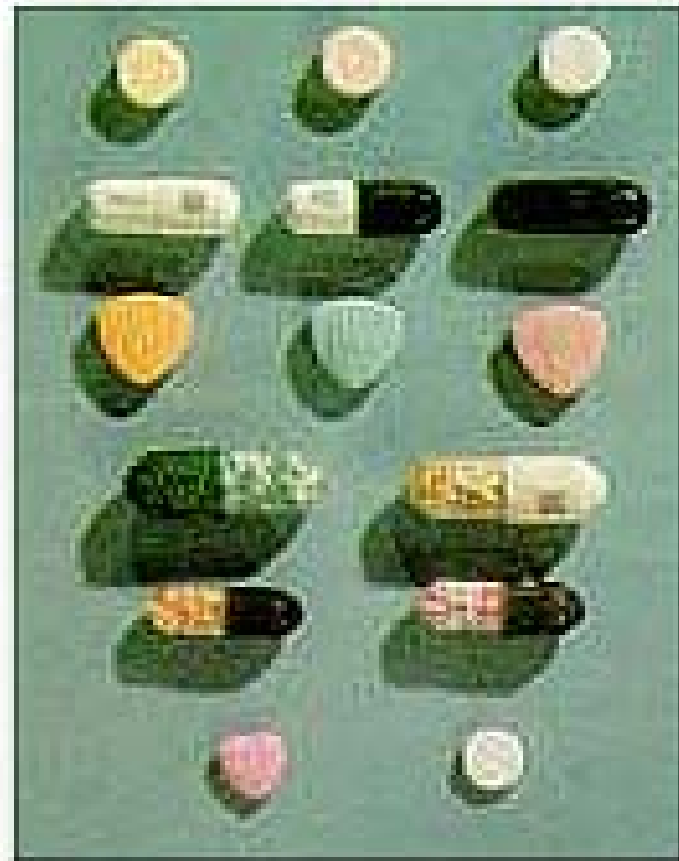
(Roth MD, J. Infect. Diseases, 2002; 185(5), 701-705)

Source : www.numedx.com

Amphetamines



Amphetamines



Amphetamines + PIs

- PIs increase by 2X to 3X amphetamine build-up in blood, by inhibiting CYP2D6 metabolism
- Serious risks of overdose especially with Ritonavir (Norvir) : hypertension, hyperthermia, seizures, arrhythmia, tachycardia and tachypnea.

Source : www.numedx.com

Crystal (Ice)



Crystal (Ice) + RTV (PI)

- Ritonavir (Norvir) increases by 2X to 3X the levels of crystal methamphetamine (**ice**) in blood.

Source : www.numedx.com

Ecstasy



Ecstasy + HIV

- One dose of MDMA (100 mg) decreased CD4+ cells by 30% within hours after a single dose.
- Two doses of MDMA, four hours apart, decreased CD4+ cells by 40%.
- Additional finding: decreased ability of CD4+ cells to fight infection.

Source : Pacifici R., Zuccaro P., et. al. Effects of Repeated Doses of MDMA ("Ecstasy") on Cell-Mediated Immune Response in Humans. *Life Sciences* 2001; 69:2931-2941; in www.thebodypro.com

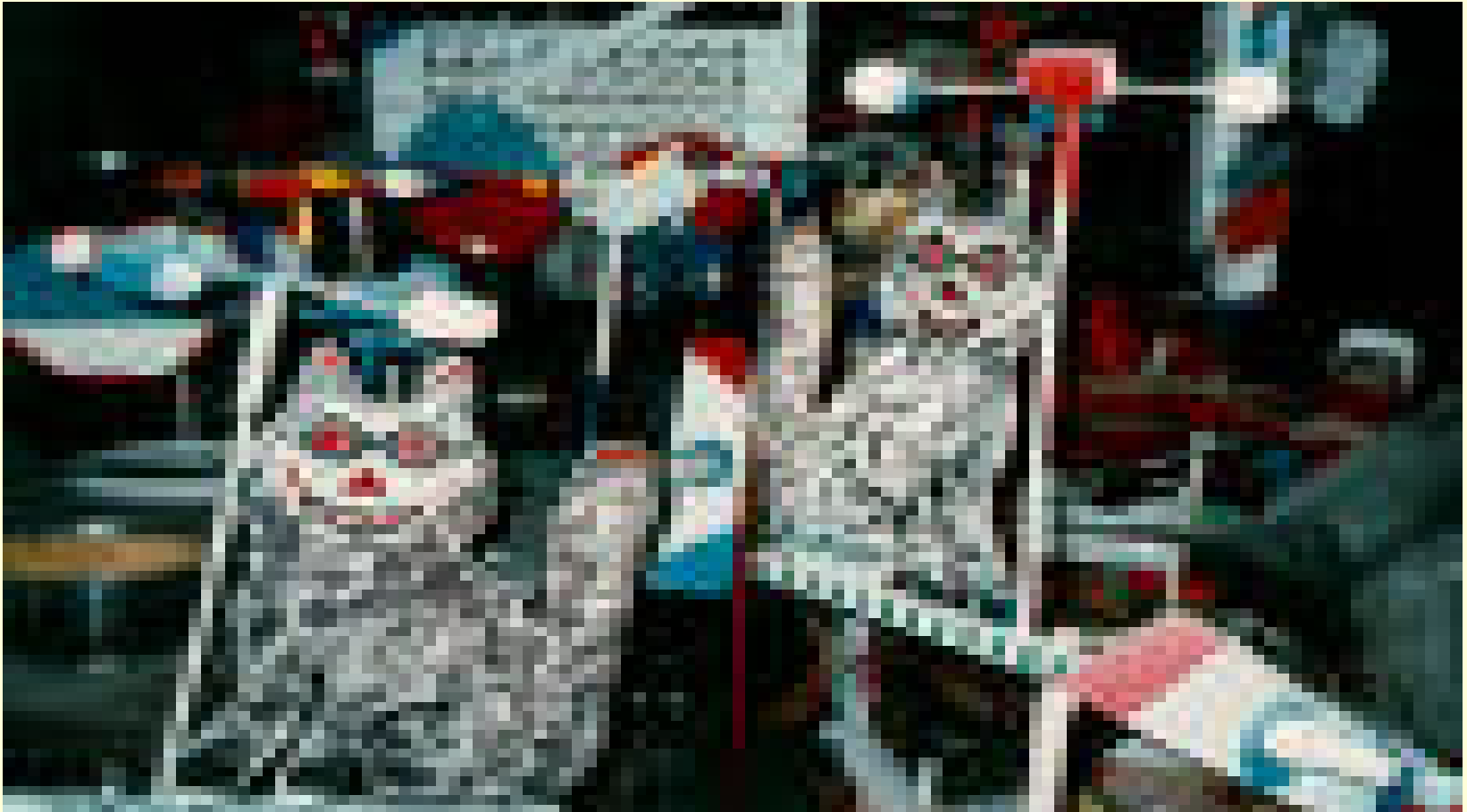
Ecstasy + PIs

- PIs increase levels of ecstasy;
- Ritonavir (Norvir) increases by 5X to 10X the levels of MDMA in blood : Risk of overdose and death.
- Potential to increase ecstasy levels with Kaletra.
- Indinavir (Crixivan) : increases risk of kidney stones due to dehydration.

(Henry JA, Fatal interactions between RTV and MDMA, Lancet, 1998; 352; 1751-1752)

Source : www.numedx.com

Hallucinogens



Hallucinogens

- Marijuana, Cannabis, Hash
- Mescaline, LSD
- PCP, Ketamine
- Glue, Solvents and Volatile Products

Marijuana



Hashish



Marijuana + PIs

- PIs increase levels of THC in blood by decreasing elimination metabolism of cannabis.
- Smaller amounts of THC may be advised for medicinal purposes.
- Marinol can be introduced at a lower dose and increased for effect.

Source : www.numedx.com

Marijuana + PIs and/or NNRTIs

- Smoked Marijuana may lower PIs and NNRTIs in blood.
- In one study, smoked THC decreased Nelfinavir (Viracept) by 17% and Indinavir (Crixivan) by 21% in blood.

(Kosel BW, The effects of cannabinoids on the pharmacokinetics of IDV and NFV, AIDS 2002; 16, 543-550)

Source : www.numedx.com

Glue, Solvents, Volatil Products



Inhalants

The chronic use of inhalants has been associated with a number of serious health problems :

- Glue and paint thinner sniffing produce kidney abnormalities while the solvents toluene and trichloroethylene cause liver damage.
- Memory impairment, attention deficits, and diminished non-verbal intelligence have been related to the abuse of inhalants.
- Deaths resulting from heart failure, asphyxiation, or aspiration have occurred.
- No known interactions between glue, solvents, volatile products and ARVs.

LSD + PIs and/or NNRTI

- PIs and/or NNRTIs CYP450 inhibitors may cause build-up of LSD
- Overdose symptoms include hallucinations, agitation, psychosis and “flashbacks”.

Source : www.numedx.com

PCP



PCP + PIs and/or NNRTIs

- PIs and/or NNRTIs may increase levels of Phencyclidine in blood
- Overdose symptoms include : seizures, hypertension, hyperthermia and rhabdomyolysis.

(Laurenzana EM, Metabolism of PCP by human liver microsomes, Drug Metab. Dispos. 1997; 25 : 557-563)

Source : www.numedx.com

Ketamine



Ketamine + ARV

- ARV builds up Ketamine in blood, especially :
- Ritonavir (Norvir) (PI)
- Nelfinavir (Viracept) (PI)
- Effavirenz (Sustiva) (NNRTI)

Source : www.numedx.com

Ketamine + RTV (PI)

- Ritonavir (Norvir) likely builds up Ketamine in blood
- Overdose symptoms : respiratory depression, loss of consciousness and hallucinations.

Source : www.numedx.com

OTHER MEDICATIONS

- Because some of our patients take more than street and/or club drugs...

REBETRON + NRTI

- Administration of nucleoside analogues has resulted in fatal and non-fatal lactose acidosis.
- Co-administration should be undertaken with caution, and only if the potential benefits outweigh the potential risks.

Source : www.rebetron.com

PEGETRON + AZT (NRTI)

- Both Peg-Interferon and Ribavirin can temporarily weaken the bone marrow.
- Use of Zidovudine (Retrovir, Combivir) may make this worse.
- Same for Pegasys

Sources : www.catie.ca

www.pegetron.com

RIBAVIRIN + NRTI

- Ribavirin has been shown in vitro to inhibit phosphorylation of AZT (Zidovudine = Retrovir) and D4T (Stavudine = Zerit), which could lead to a decrease in ARV activity.
- The concomitant use of Ribavirin and AZT of D4T should be avoided

Source : www.pegasys.com

RIBAVIRIN + ddl

- **NOT RECOMMENDED**
- Ribavirin increases ddl (Didanosine = Videx) activity in blood.
- Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis and symptomatic hyperlactatemia/ lactic acidosis has been reported in clinical trials.

Source : www.pegasys.com

Viagra + PI

- PIs, Ritonavir (Norvir) in particular, increase by 4X the levels of Sildenafil Citrate (Viagra) in blood.
- If indicated, start with Viagra 25 mg instead of usual 50 mg dose in conjunction with PIs.

Source : www.viagra.com

Viagra + Poppers

- Be sure not to use poppers if you take Viagra, Levitra or Cialis.
- Poppers (amyl nitrate or butyl nitrate) increase levels of these drugs, lowering your blood pressure enough to cause serious, even lethal, reactions.

Anabolic Steroids + RTV (PI)

- Ritonavir (Norvir) increases by 2X to 3X the levels of anabolic steroid in blood.

Source : www.numedx.com

For more information

- www.numedx.com, in *Quality of Life : Lifestyles, Risky Cocktails*
- www.thebodypro.com
- www.harmreduction.org
- www.catie.ca
- All medication Websites
(ex. : www.norvir.com)