Management of HIV+ IVDUs

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St. James's Hospital Dublin

- Approx 4500 actively attending HIV+ patients.
- 25% of patients registered for care have a history of IVDU, most receiving methadone maintanance therapy.
- 148 of those have a CD4 count of <350 and are not receiving ARVs
- 77% of all HIV+ hospitalisations in our department are in IVDUs, secondary to both IVDU related infections, DVTs, HIV and HepC related complications.

Personal Communication Dr. Helen Tuite

To set the scene

- Compared with other risk groups, injection drug users are twice as likely not to be receiving ART and this increases to three times if they are not enrolled in a drug treatment programme.

- Only 40% of injection drug users eligible for antiretroviral therapy are receiving it, and only 37% of this group are adherent with therapy

- THIS HAS NOT CHANGED OVER TIME!!!!!

- *Strathdee SA, Palepu A, Cornelisse A, et al. Barriers to use of free antiretroviral therapy in injection drug users. JAMA. 1998;280:547–549.*
- *3. Celentano BD, Vlahov D, Cohn S, Shadle VM, Obasanjo O, Moore RD. Self reported antiretroviral therapy in injection drug users. JAMA. 1998;280:544–546.*

The effect of injecting drug use history on disease progression and death among HIV-positive individuals initiating combination antiretroviral therapy: collaborative cohort analysis.
HIV Med. 2012; 13(2):89-97 (ISSN: 1468-1293)

Murray M et al. British Columbia, Canada
Large statistical analysis of 6269 IVDUs and 37,774 non IVDU's

- Compared Hazard ratios for AIDS and death
- Overall mortality rate was higher in IVDUs
  2.08 vs 1.04 per 100 person years
- Greater risk of death from liver, violence, and non-HIV deaths
- Greater association between lower CD4 count and
  risk of AIDS diagnosis and death in IVDUs

Issues

- Psychosocial
- Adherence
- DOT
- ART and Methadone
- HepC/HIV coinfection

Psychosocial

- Manipulative
- Violent/threatening behaviour
- O/D(deliberate or accidental)
- Withdrawal symptoms
- Psychosis/depression
- Seizures(benzo withdrawal)
- AMA

Hospital In-Patient Contract

Dear [ ]

The Board of Management of St James's Hospital (the "Hospital"), wishes to advise you that your recent improper actions and behaviour is in breach of Hospital policies and is unacceptable. This is jeopardising your current care plan and has had a detrimental effect on the ward and has prevented our staff from doing their clinical duties and thus interfering with their care for other patients. This decision has been reached as you have not been compliant with the Hospital's policies regarding your stay as an in-patient.

The Hospital has a strict '*zero tolerance*' policy in relation to behaviour that challenges and any future such behaviour will not be tolerated.

In light of the above, and to ensure your continued stay at the Hospital whilst arrangements continue to be made for your timely discharge, we require you to reconsider your attitude to our attempts to address your clinical and social needs, and as such, that you seek clinical care in a spirit of genuine co-operation and compliance by adhering to the Hospital policies below, should you wish to remain an in-patient with us:

1. **Drinking alcohol is not permitted in the Hospital or on its grounds**
   Any further breach of hospital policy will result in your immediate discharge from the Hospital.

2. **Illegal Drug Use Policy**
   St James's Hospital has a responsibility to report any incidence of illegal or un-prescribed drugs / substance abuse to An Garda Síochána. A further breach of hospital policy will result in your immediate discharge from the Hospital.

3. **Anti-Social Behaviour Policy**
   In the interest of the safety and wellbeing of other patients and staff, anti-social or aggressive behaviour or any behaviour that is deemed inappropriate in nature will not be tolerated, and will be reported to An Garda Síochána. Any future incident will result in your immediate discharge from the Hospital.

The aim of this Patient Contract is to safeguard you, our staff and other patients and to optimise your treatment and care in the Hospital. Confidentiality is maintained at all times with regard to your treatment. This contract applies as follows:

Substance Misuse

- I will not use drugs or un-prescribed medications during my stay in hospital.
- I will not use alcohol during my stay in hospital.
- I will not deal in any drugs be they illegal or prescribed or alcohol during my stay in hospital or while on its grounds.
- I will give supervised urine samples when required.
- I agree / give permission to allow hospital staff to search me or my possessions on request.

OSPIDÉAL SAN SÉAMAS
ST. JAMES'S HOSPITAL

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St. James's Street, James's Street Dublin 8
+353 1 410 3000 www.stjames.ie

I, [ ] confirm that I have read or that I have had read to me the above and I understand that if I fail to comply with the above referred to policies during the remainder of my stay at the Hospital, that I will forfeit my right to a bed on the ward and will be immediately discharged from the Hospital campus.

Signed ..... Dated 2019

[ ] (Patient)

In circumstances where this contract has been read to the patient but they have refused to sign, the Hospital accepts that this is a unilateral contract and shall act in the terms prescribed above, based on the patient's future conduct.

Signed ..... Dated 2019

[ ] (CNM)

Problem :Non- adherence

What are the contributing factors?

1. Stigma
2. Psychiatric illness
3. Social issues
4. Physician perception
5. Drug use
6. All of the above

AIDS Behav. 2019 Apr;23(4):1084-1093. doi: 10.1007/s10461-018-2307-y.

Client and Provider Perspectives on Antiretroviral Treatment Uptake and Adherence Among People Who Inject Drugs in Indonesia, Ukraine and Vietnam: HPTN 074.

Go VF[1], Hershow RB[2], Kiriazova T[3], Sarasvita R[4,5], Bui Q[6], Latkin CA[7], Rose S[8], Hamilton E[8], Lancaster KE[9], Metzger D[10], Hoffman IF[11], Miller WC[9].

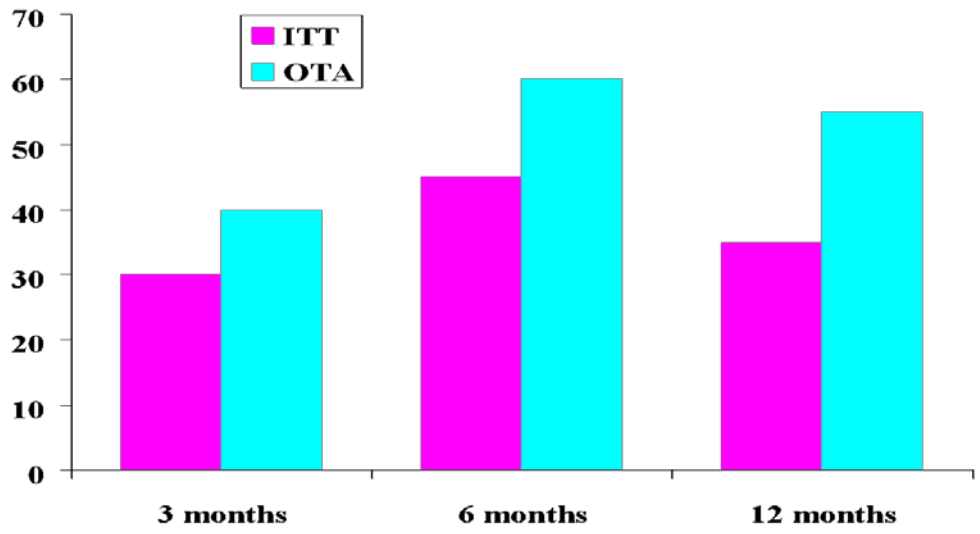
62 participants
25 providers :37 IVDUs
both recognised barriers ,access to clinic ,finances,side effects,lack of HIV and ART info
Providers emphasised lack of motivation due to drug use
their language reflected stereotypes about drug users

Answer :The DOT Option

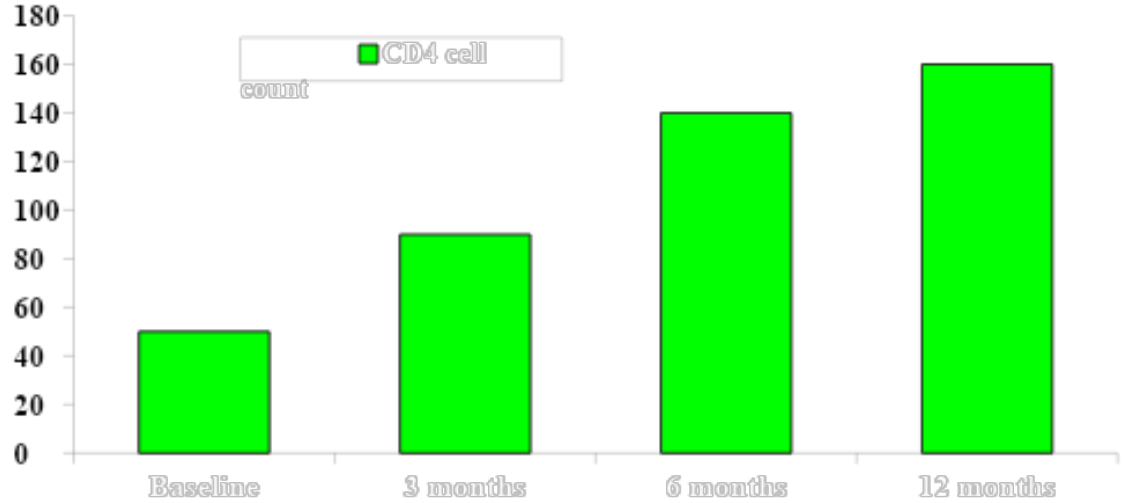
DOT in IVDUs St. James' Hospital, Dublin

- N=39pts [24M/15F] ; ART naïve 49%
- Mean HIV RNA 5.35logs
- Mean CD4 251X10^6/L

%BLD vs Time (<50cpm)



CD4 cell count vs Time



Patient	39	35	31	27
Attending	100%	90%	79%	69%

Methadone maintenance therapy associated with adherence to HAART [p=0.04]

Clarke et al AIDS Read. 2002 Jul;12(7):312-6.

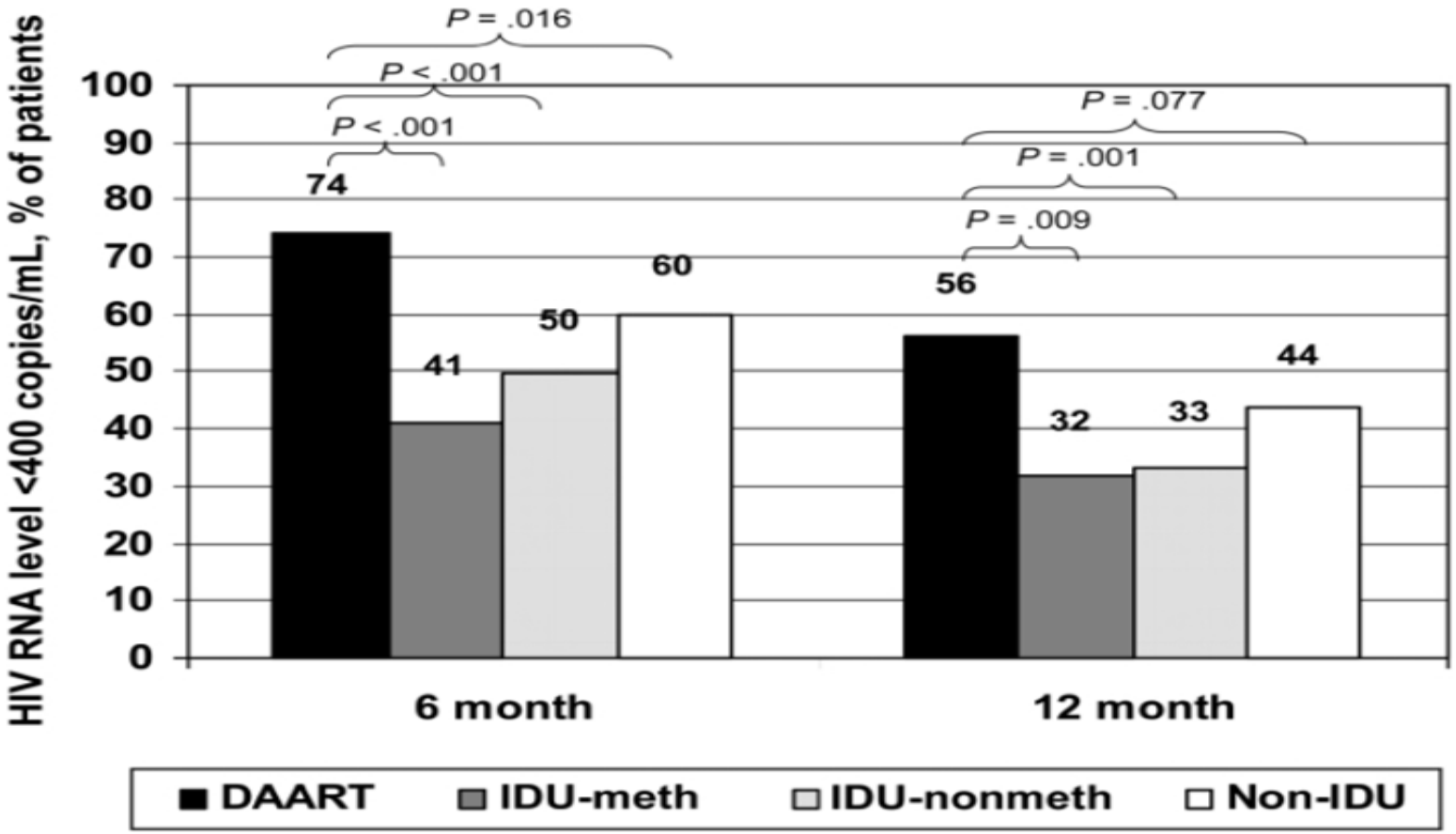
DOT study in Johns Hopkins

- DOT at 3 urban clinics
- Enrolled 82 IVDUs and given DOT
- 3 comparison groups
  - Hx IVDU and on methadone
  - Hx IVDU and no methadone
  - No history of IVDU
- Mean increase in CD4 count was

– DOT group	74	56% <400
– Hx IVDU and on methadone	21	32%<400
– Hx IVDU and no methadone	33	33%<400
– No history of IVDU	84	44%<400

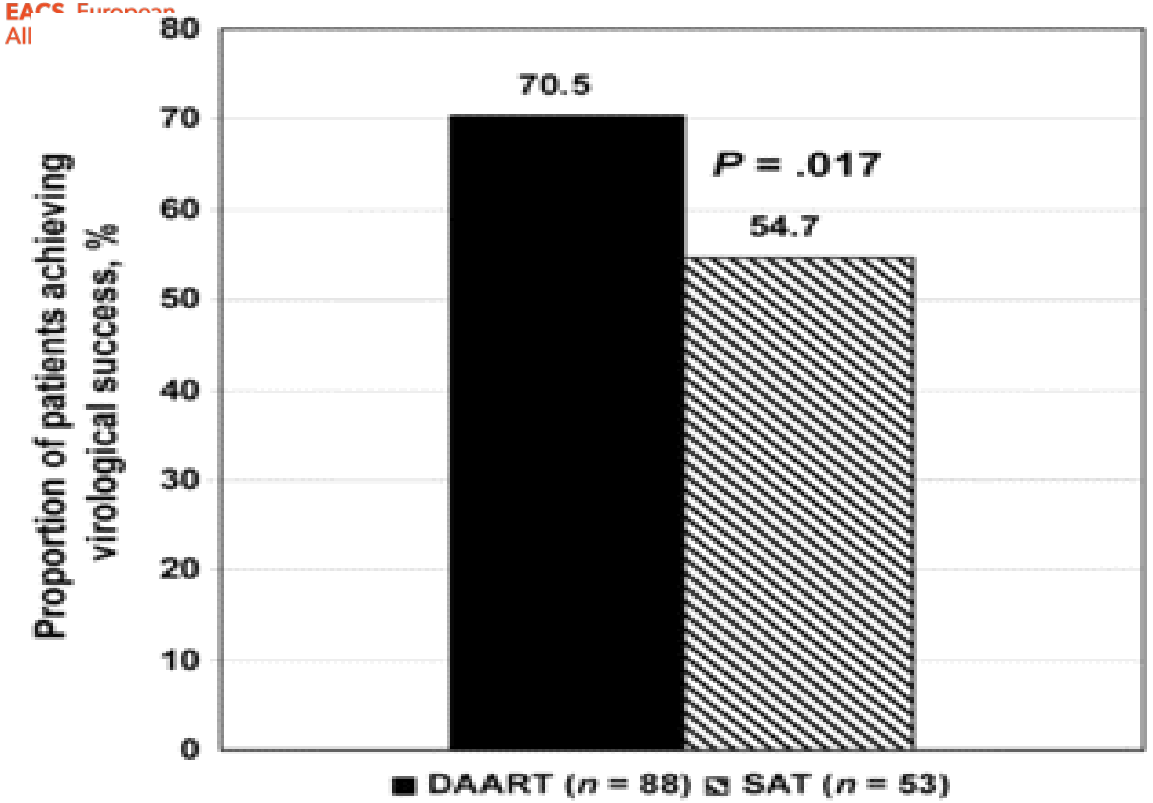
Lucas GM et al. Directly Administered Antiretroviral Therapy in Methadone Clinics Is Associated with Improved HIV Treatment Outcomes, Compared with Outcomes among Concurrent Comparison Groups Clinical Infectious Diseases 2006; 42:1628–35

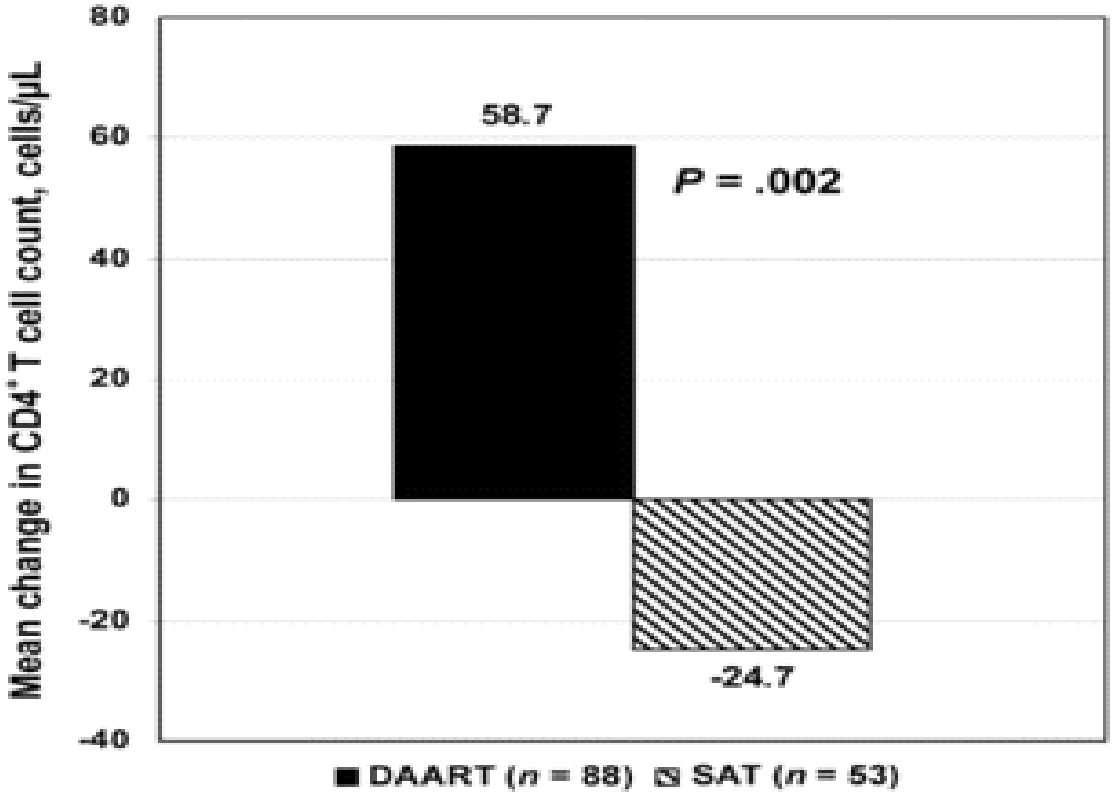
% of patients achieving viral suppression at 6 months



Lucas GM et al. Directly Administered Antiretroviral Therapy in Methadone Clinics Is Associated with Improved HIV Treatment Outcomes, Compared with Outcomes among Concurrent Comparison Groups Clinical Infectious Diseases 2006; 42:1628–35

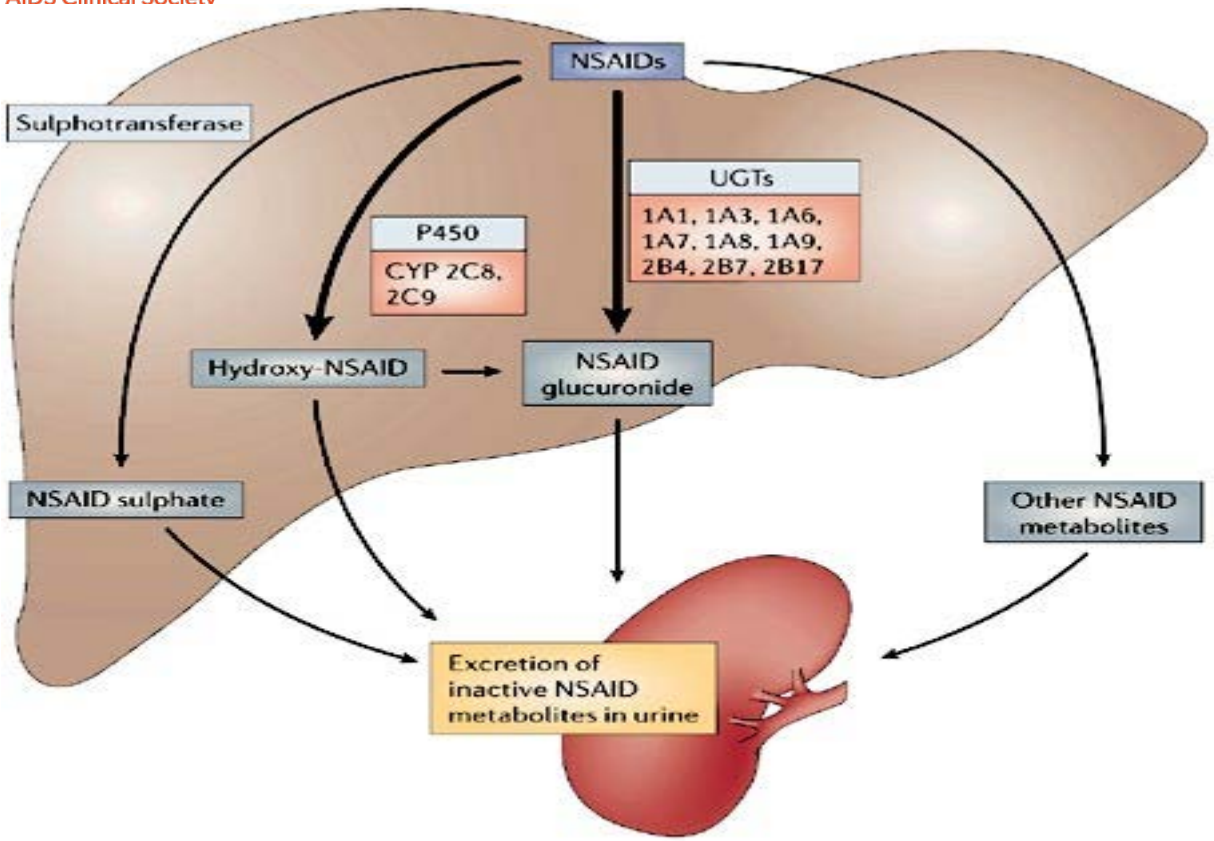
A (Randomised) DOT study

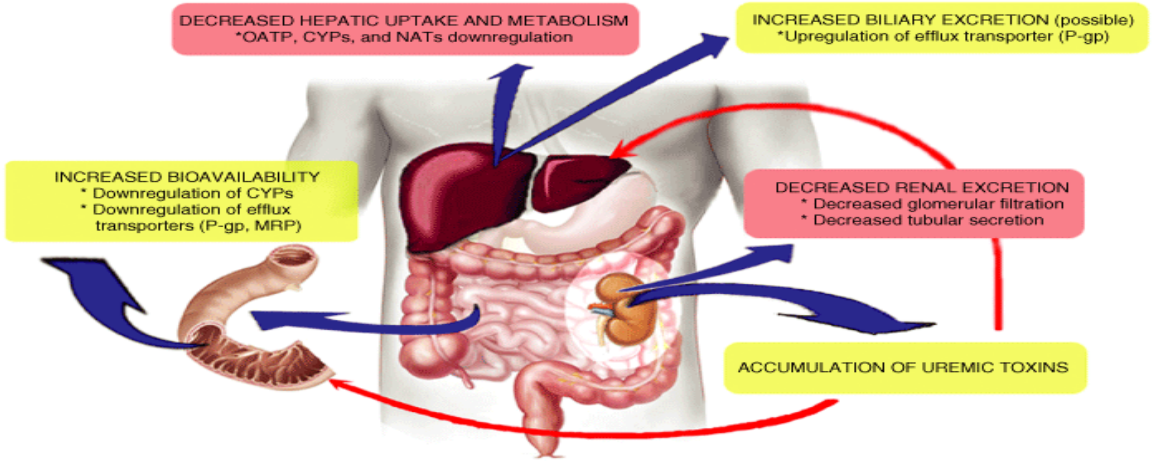




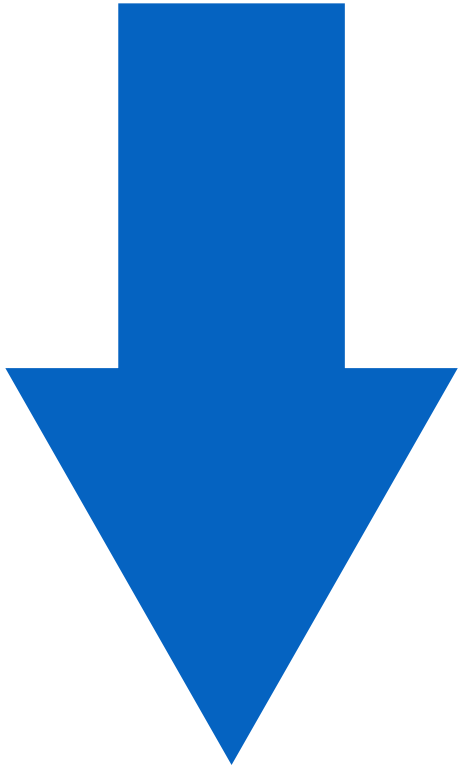
Altice FL, Friedland GL et al. **Superiority of Directly Administered Antiretroviral Therapy over Self-Administered Therapy among HIV-Infected Drug Users: A Prospective, Randomized, Controlled Trial** ***Clinical Infectious Diseases. 2007: 45:6:770-8***

Pharmacokinetic Issues with Antiretroviral therapy

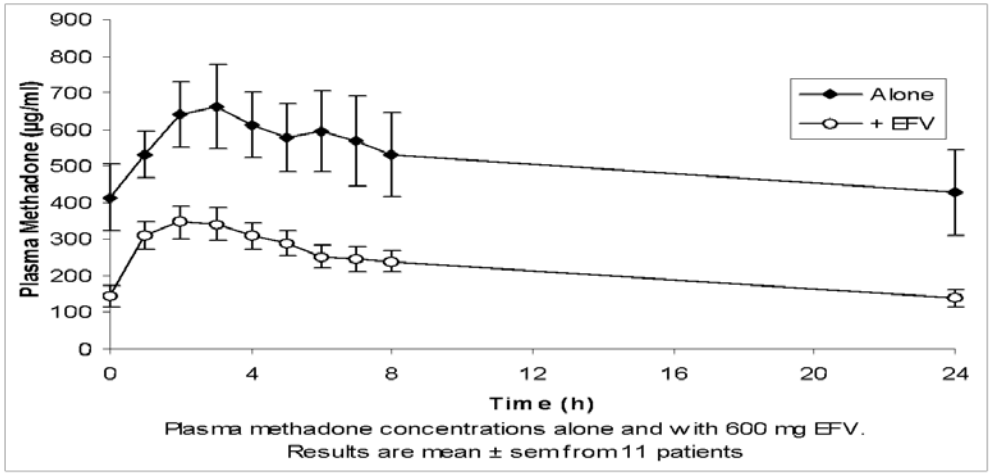




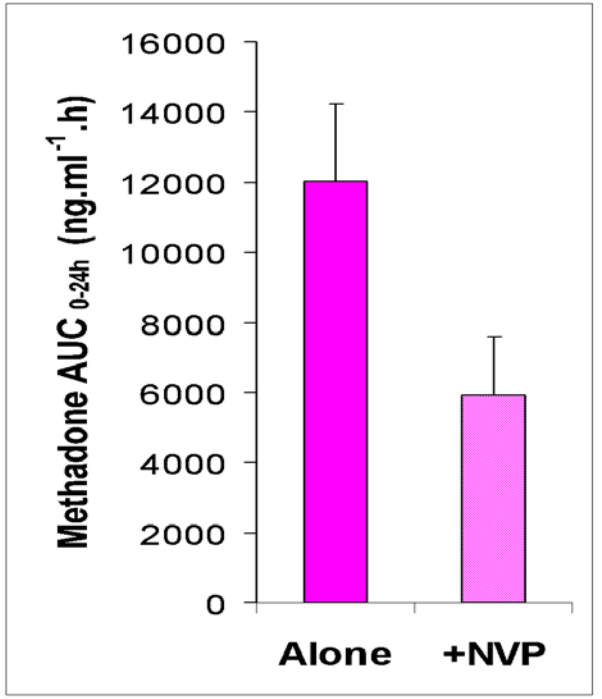
Interactions between methadone and HIV medications

Drugs	Effect on Methadone
Rifampicin	
Phenytoin	
Phenobarbitone	
Carbamazepine	
Rifabutin	
Efavirenz	
Nevirapine	
Nelfinavir *	
Lopinavir *	
Ritonavir	
Cobistat	

Previous methadone ART studies

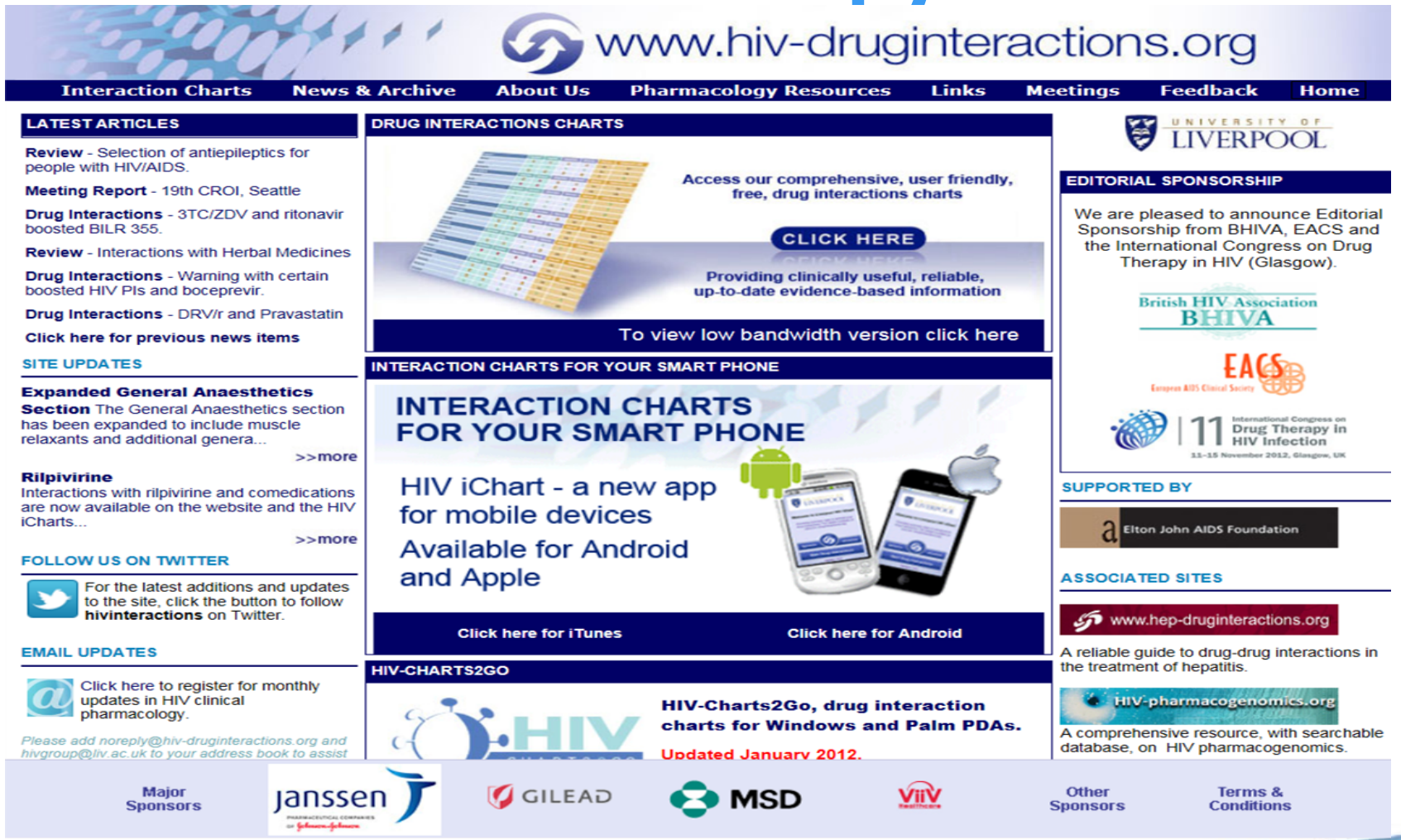


I-Methadone+EFV



II-Methadone+NVP

Pharmacokinetic Issues with Antiretroviral therapy



Interaction between Efavirenz and methadone/Buprenorphine

Factor	Methadone	Buprenorphine
Baseline opioid dose, mg/day	80 (28)	17.2 (1.9)
Post-efavirenz opioid dose, mg/day	120 (10)	17.2 (1.9)
Opioid dose increase, %	50	0
Time to opiate withdrawal, weeks	1 (.84)	Not applicable
Time to stable opioid dose, weeks	4 (4.2)	0
Baseline OOWS score	0.7 (1.1)	0
Post-efavirenz OOWS score[a]	5 (3.3)	0.10 (0.3)

NOTE. Data are mean (SD) except where noted. OOWS, Objective Opiate Withdrawal Scale.

[a] $P = .0005$.

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» In a new window

» Download as PowerPoint Slide

Table 1

Comparison of the effect of efavirenz on opioid dependence pharmacotherapy treatment with either methadone or buprenorphine.

E F McCance-Katz Clinical Infectious Diseases 2005 4 (1)S89-95
Treatment of Opioid Dependence and Coinfection with HIV and Hepatitis C Virus in Opioid- Dependent Patients: The Importance of Drug Interactions between Opioids and Antiretroviral Agents

Other significant Drug-drug Interactions – darunavir /r and Atazanavir/r methadone

- **Darunavir and methadone**
  - 16 HIV negative volunteers on stable methadone maintanance programmes.
  - Mean baseline methadone dose was 55-200 per day
  - Measured Cmin, Cmax, AUC after introducing darunavir/ritonavir to their methadone therapy.
  - Found reductions of 15,24,30%
  - No dose adjustments required

Seker et al. J Clin Pharm 2011:53:271-8

Atazanavir and methadone.

- 16 Healthy volunteers recruited HIV negative
- All on stable methadone maintanance therapy
- No significant changes in PK data
- No significant clinical symptoms of withdrawal
- No dose adjustments required.

Friedland G et al. AIDS 2005:19:1635-41

Other significant Drug-drug Interactions – Etravirine /Rilpivirine and methadone

A Pk and PD study of the concomitant administration of methadone and Etravirine or Rilpivirine in HIV negative volunteers

Etravirine

- 16 HIV negative volunteers
- No clinical withdrawal symptoms
- No significant drug PK interactions
- No need for dose adjustment

J Clin Pharm March 2008 Scholler-Gyure M et al

Rilpivirine

- HIV negative volunteers.
- All receiving stable methadone maintenance therapy.
- Reduction in AUC of methadone 16%, Cmax 13%, Cmin 21%
- No dose adjustments required
- No clinical symptoms of withdrawal.

Crauwels HM et al. PK interaction Workshop 2010 Abstract 33

Other significant Drug-drug Interactions – Raltegravir and methadone

- Anderson et al
  - JCP 2010:50 (12) 1461
  - Effect of Raltegravir on the PKs of methadone
  - N=12 HIV negative volunteers
  - No change in PK of methadone and no withdrawal symptoms

- Tossonian HK et al – ACTUAL HIV+ PATIENTS!!!!!
  - 18th Annual Canadian conf on HIV/AIDS research
  - N=20 inner city clinic in Vancouver in a DOT programme
  - At a mean of 100 days follow-up, no change in methadone dose required.
  - No clinical symptoms of withdrawal.

Crauwels HM et al. PK interaction Workshop 2010 Abstract 33

ARVs and Heroin

- Commonly abused derivatives of the opium poppy include heroin (metabolized by plasma esterases to morphine), morphine (metabolized by glucuronidation), and codeine (metabolized by glucuronidation).

- Although ARVs are also metabolized by glucuronidation, no interactions between them and heroin, morphine, and codeine have been reported.

ARVs and Cocaine

- Cocaine is a known immunotoxic agent,
  - decreasing CD4 production x 3
  - increasing HIV reproduction X 20-fold.
- Cocaine is metabolized by plasma and hepatic esterases. However, about 10% is metabolized by CYP450 enzymes, **including CYP3A4**.
- Chronic cocaine administration has been shown to induce CYP3A4 in rodents.

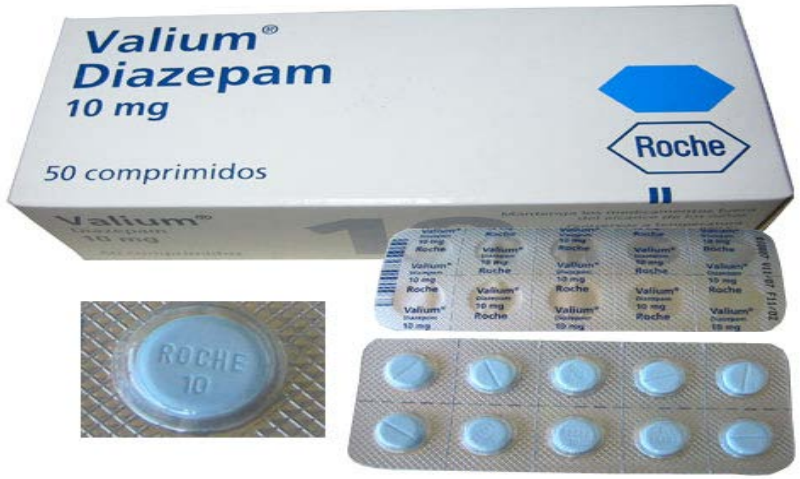
- If cocaine induces CYP3A4 in humans as well, it may decrease levels and effectiveness of the many ARVs that are CYP3A4 substrates, including most NNRTIs and PIs. P-glycoprotein, an efflux transporter, is increased both by HIV disease and chronic cocaine use. For ARVs that are transported by p-glycoprotein, such as abacavir, this may result in increased excretion, and subtherapeutic ARV levels.

ARVs and Ecstacy

- Amphetamines and ecstasy are primarily metabolized **by CYP2D6** [5].
- Combining even a small dose of ecstasy with the CYP2D6 inhibitor ritonavir has increased and prolonged the effects of ecstasy. In one report, a man died after drinking beer and taking ecstasy after ritonavir was added to his ARV regimen.

- Another case report described a near-fatal reaction (unresponsive, shallow respirations) in a 29-year-old man who took his usual dose of ecstasy and gamma-hydroxybutyrate (GHB) after having a change in ARVs to a PI/r

ARVs and Benzodiazepines



- Several commonly abused benzodiazepines are metabolized by CYP3A4.
- These include alprazolam (Xanax), clonazepam (Klonopin), diazepam (Valium), and flunitrazepam (Rohypnol)
- . CYP3A4 inhibitors cause their levels to rise, resulting in possible toxicities such as oversedation.
- Conversely, when CYP3A4 inhibitors are stopped, patients may have benzodiazepine withdrawal symptoms.
- Likewise, CYP3A4 inducers may cause withdrawal symptoms and dose escalation (eg, medication seeking) to avoid withdrawal.

Cardiac issues – prolonged QTC

- A 34-year-old male patient receiving antiretroviral therapy, methadone and flurazepam presented to the emergency room following collapse with associated loss of consciousness.
- Cardiac monitoring demonstrated marked Q-T prolongation followed by the cardiac arrhythmia, torsade de pointes. The patient made a full recovery following withdrawal of the antiretroviral therapy and a reduction in methadone dose.
- Methadone is a recognised cause of this potentially fatal cardiac arrhythmia which is more likely to occur when methadone metabolism is inhibited by drugs such as HIV protease inhibitors.
- Especially associated with higher doses of methadone
- Patients usually receiving multiple other potential causes of arrythmias

Methadone induced torsade de pointes in a patient receiving antiretroviral therapy. Irish MJ 2007:100:631-2

Presented to The Emergency Dept

- 2 week history of dizzy spells
  - lasting a few seconds
  - no blackout
  - no visual symptoms, no headaches
- No history of seizures
- No family history of seizures
- No alcohol intake for 2 weeks (8 units)
- 2 weeks and 1 month previously, took benzodiazepines
- Injected cocaine 17 days previously
- Eating well

Examination NAD

Hb 13.4
Plt 189
WCC 2.7
Neut 1.0
Lymph 1.3

Medications

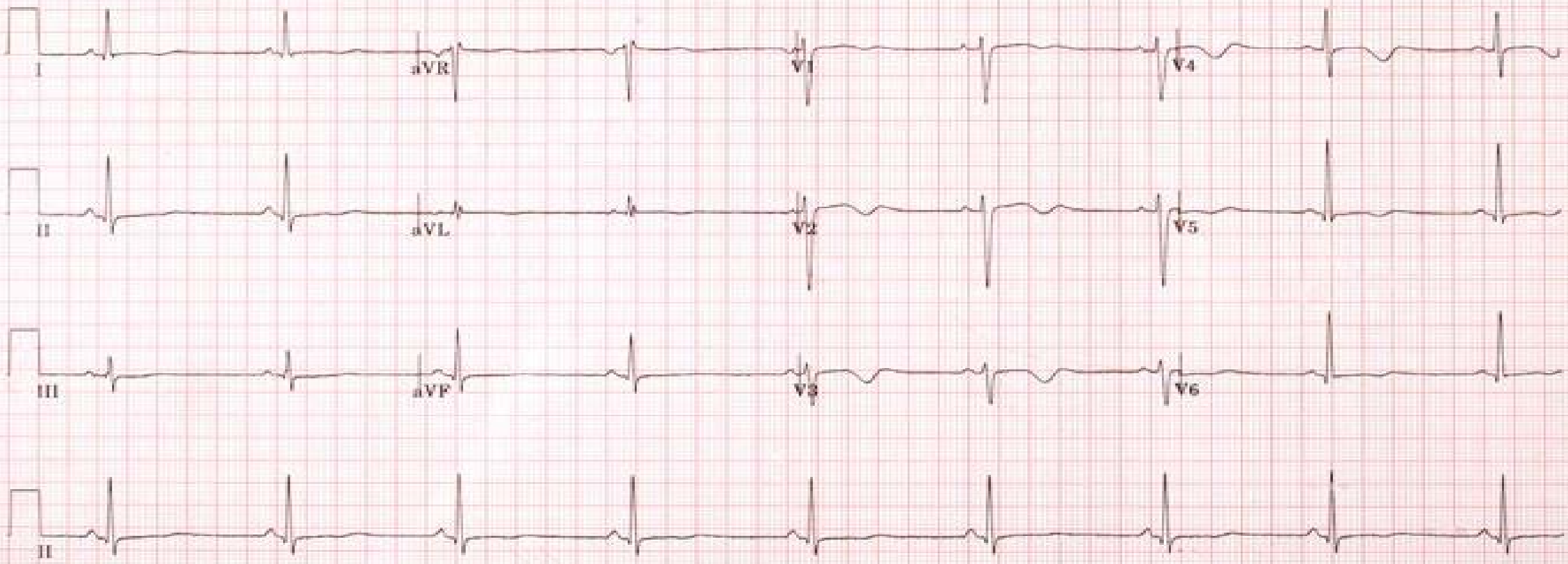
- Methadone 120ml od
- Zolpidem 20mg nocte po
- Mirtazepine 30mg nocte po
- Co-trimoxazole 960mg
- Truvada/ PI /r once daily

- Grossly abnormal ECG
- T wave biphasic and long QT
- Echo normal
- Clinical episode of progression: seizure
- Maternal Grandfather sudden death age 46

33years
Female

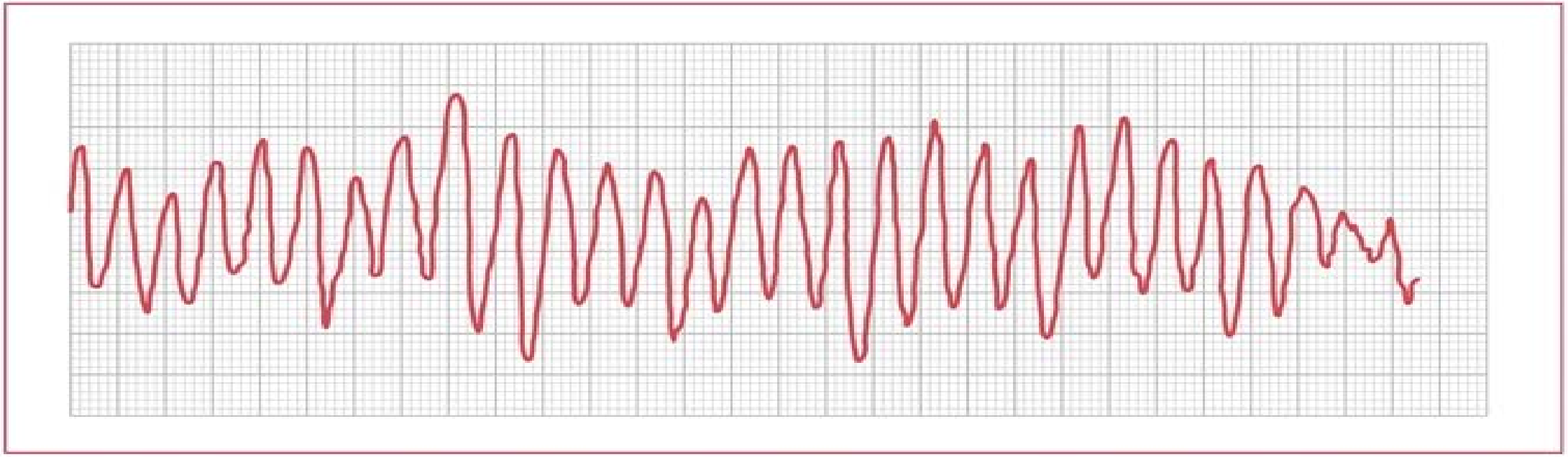
Vent. rate	52	bpm
PR interval	126	ms
QRS duration	92	ms
QT/QTc	544/505	ms
P-R-T axes	54 39 45	

Unconfirmed



150 Hz 25.0 mm/s 10.0 mm/mV 4 by 2.5s + 1 rhythm ld MAC5K 008B 12SL™v237

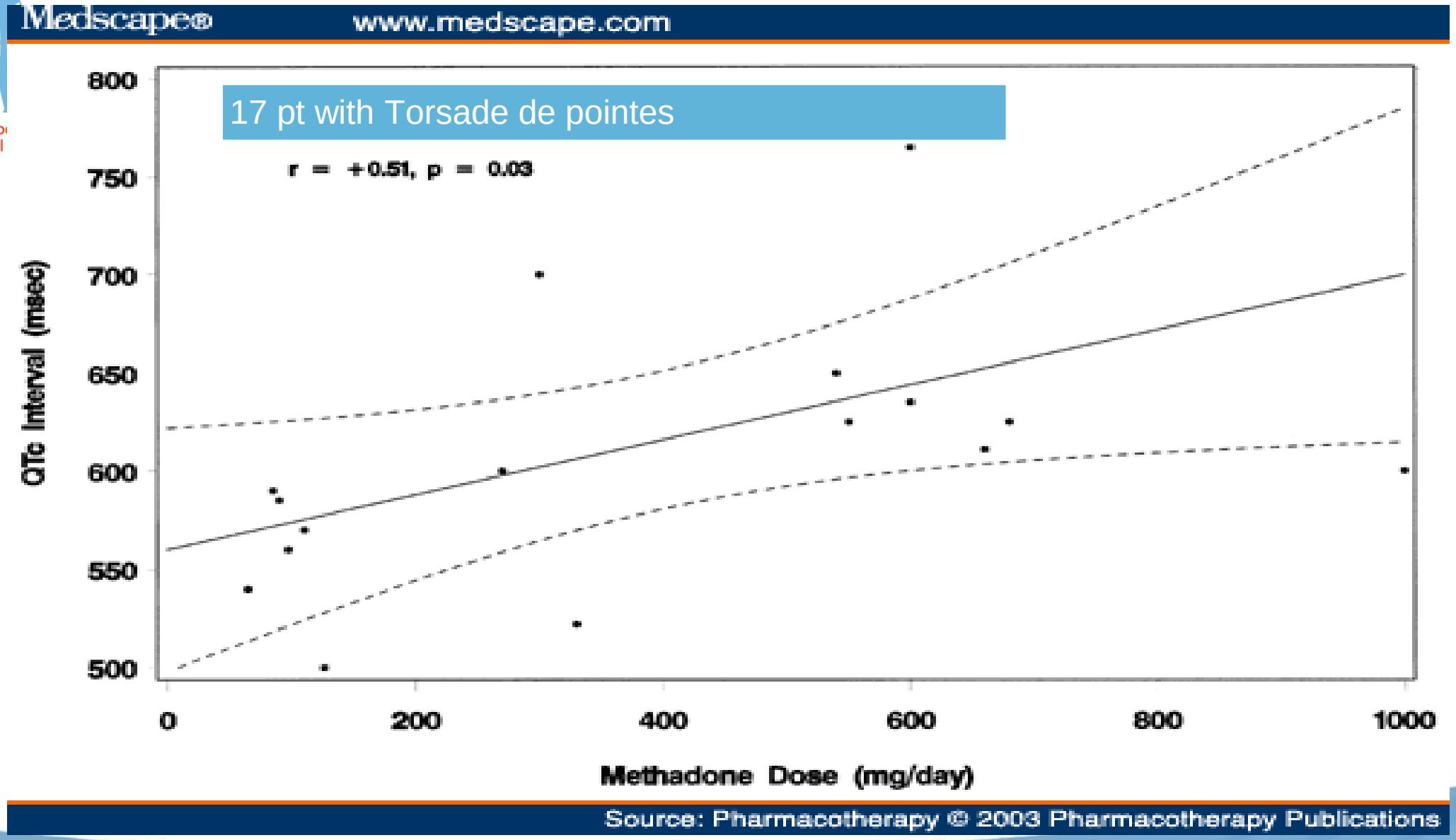
Torsades de pointes



What would you do?

1. D/C ART
2. Serial ECGs
3. Echo
4. Cardiology opinion
5. Methadone levels
6. Monitor electrolytes
7. D/C , reduce Methadone

Dose-Related Effects of Methadone on QT Prolongation in a Series of Patients With Torsade de Pointes



Krantz et al from Pharmacotherapy

Torsades de Pointes

- Predisposing risk factors for QT interval prolongation
  - **older age, female sex, Bradycardia**
  - **baseline prolonged QT interval[?]**
  - electrolyte abnormalities (including hypokalemia and hypomagnesemia)
  - congestive heart failure
  - ion-channel polymorphisms
- Drug-drug interactions:
  - Inhibition of cyto p450 can decrease metabolism of the protease inhibitors
    - increasing the possibility of QT interval prolongation
  - Ritonavir/Cobistat

Current Treatment options for IVDUs currently with HIV infection

- Stable re IVDU on a opioid replacement programme.
- Once daily combination either self-administered or as DOT
- Minimal potential side effects
- No drug-drug interactions
- Preferably no concurrent Hepatitis C infection
- Preferably non-smoker
- Need to maintain good general health and focus on other medical issues that may arise as patients live longer with HIV infection.