THE LANCET
HIV

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Krupitsky E, Blokhina E, Zvartau E, et al. Slow-release naltrexone implant versus oral naltrexone for improving treatment outcomes in people with HIV who are addicted to opioids: a double-blind, placebo-controlled, randomised trial. *Lancet HIV* 2019; published online March 14. http://dx.doi.org/10.1016/S2352-3018(18)30362-X.

Appendices

Appendix 1. Informed Consent Quiz

Version 1.0 1/28/10

Adherence to HIV Therapy in Heroin Addicts: Oral vs. Extended Release Naltrexone

Participant Study Number _ _ _ _ Date: _ _ / _ _ / _ _

Circle the best choice

True False 1. If I start the study, and I change my mind and decide NOT to do this research study, I can stop my participation at any time.

True False 2. If I give consent to join this study, I will be guaranteed to get the Naltrexone Implant (Prodetoxon®) for 48 weeks.

True False 3. The most common side effects of naltrexone are nausea, headache, dizziness, fatigue, insomnia, anxiety, and sleepiness, but not everyone experiences these things.

True False 4. If I participate in this study I will be asked to go to other treatment services such as counseling or group therapy.

True False 5. If I drop out or get discharged from the study the researchers will still want to see me for follow-up evaluations.

True False 6. If I join the study, I might get either a 48 week course of oral naltraxone treatment or a 48 week course of naltrexone as an implant. I don't get to pick which treatment condition that I get, and the research staff doesn't get to pick it either.

True False 7. If I join this study, I will not be started on the study medication until I pass a naloxone test, which means that I have no signs or symptoms of opioid withdrawal.

True False 8. If I join this research study, I will be asked to keep appointments, take medication only as directed, and try not to use drugs or medications that are not prescribed by a study doctor.

True False 9. I am being asked to join this study because I want to stop using opioids.

True False 10. If I choose not to participate in this study, I can still receive the other kinds of treatment that are available in this area.

_____ Participant's Name (Print)

_____Participant's Signature

Appendix 2

January 17, 2012 vs. 1(c)

UNIVERSITY OF PENNSYLVANIA/PAVLOV HIV STUDY
CONSENT TO PARTICIPATE IN RESEARCH

Adherence to HIV Therapy in Heroin Addicts: Oral vs. Extended Release Naltrexone

Principal Investigator: United States	George Woody M.D. University of Pennsylvania Public Ledger Building 150 S. Independence Mall West Philadelphia, PA
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On-Site Principal Investigator: Russia	Dmitri Lioznov, M.D. Center for Chronic Viral Infections Research, Pavlov State Medical University, St.Petersburg, Russian Federation
24-Hour Emergency Contact:	Crisis Intervention for Medical and Psychiatric Emergency: 296-9905 (Leningrad Regional Center of Addictions); 973-5396 (Pavlov State Medical University)

Why am I being asked to volunteer?
You are being asked to participate in a research study because you have been addicted to heroin or other opioids within the past year and are starting or have had past antiretroviral treatment (ART) for HIV. The study will be conducted at Pavlov State Medical University Addiction Treatment Unit, Botkin Hospital, Leningrad Region Addiction Treatment Center and Leningrad AIDS Center. The study is sponsored by Pavlov State Medical University in St. Petersburg and the National Institute on Drug Abuse in the U.S. Drs. Evgeny Krupitsky, Edwin Zvartau, and Dmitri Lioznov are the Study Physician at the St. Petersburg and Leningrad Region sites, and Dr. George Woody is the Principal Investigator from the University of Pennsylvania in the U.S.

This consent form explains the study but may contain words or ideas you do not understand so please ask the doctor, or research or treatment staff if you have questions or need more information. Before you can make a decision about participating in the study you will need to know what it is about, the possible risks and benefits of being in it, and what you will have to do if you agree to participate. The research team will explain the study in detail, answer questions you may have, and give you this consent form to read and sign if you agree to participate.

Participation in the study is **completely voluntary** and if you choose to participate and later change your mind, you can drop out at any time and will not lose any treatment opportunities or benefits you might otherwise receive.

Listed below are some words and abbreviations you need to know while reading this

consent form:

Opioid: Opioids are natural and man-made drugs used for pain relief and include drugs such as morphine and heroin.

Oral Naltrexone (ON): Oral naltrexone blocks the physical and subjective effects of opioids if taken as directed, which for this study is one 50 mg tablet per day.

Implant Naltrexone (IN): Naltrexone can also be given as an implant. Prodetoxon ® is the implant that will be used in this study. It contains 1000 mg of naltrexone that is slowly released into your body after it is inserted under the skin of your abdominal wall by first making a small cut that is closed with 2-3 sutures. Prodetoxon ® can block the effects of opioids for 3 months.

Naloxone (NX): A drug that, like naltrexone, blocks the effects of opioids. It works only if it is injected and lasts about 30 minutes. It is used in hospitals and by emergency services to reverse the effects of a heroin or other opioid overdose. It will cause withdrawal if injected into someone who is currently physically dependent on opioids and will be administered to you as a way of making sure that you are not physically dependent on heroin or other opioids before you are given oral or implant naltrexone.

Placebo: A substance that looks like a real drug but has no pharmacological effects.

ART: antiretroviral treatment medication for HIV infection

What is the purpose of this research study?

The purpose of this study is to compare naltrexone implant (IN) with oral naltrexone (ON) for improving your response to ART. Your response will be determined by measuring the amount of AIDS virus your blood. Taking ART exactly as prescribed will increase your chances for keeping the amount of virus at a low level and preventing your immune system from being damaged by the virus. Persons who are addicted to heroin or other opioids often do not take medications as prescribed and we think that preventing relapse to addiction will help avoid that problem. Both IN and ON will prevent relapse if taken as directed, and we want to see which one works best for preventing relapse and helping you take ART as prescribed so as to keep the amount of virus in your blood as low as possible.

How long will I be in the study?

The study will last 48 weeks.

How many people will be in the study?

200 individuals are expected to participate.

What am I being asked to do?

The study has three phases:

Phase 1 - PRE-SCREENING

During pre-screening the following will happen:

You will be approached by clinical or research staffs around the time you begin or restart ART and asked if you are interested in the study. If you express interest, a study technician or assistant will describe it in

more detail and if you continue to express interest, you will be referred to a narcologist who will again explain the study in detail, answer any questions you may have, review the consent form and have you sign it after confirming that you understand the study and what will be required if you decide to participate. When you have signed the consent you have some additional examinations and tests at one of the two addiction programs to see if you qualify for the study.

Phase 2 – SCREENING

During this phase you will:

Have a medical history and physical examination

Be asked to give us information so we can find you if you miss an appointment. To help with this, you will be asked to name several people who might help us find you. If we need to contact these people, they will not be asked questions about your health, drug use, or any other personal information. The staff member who calls will only ask that you return a call to the number provided and not give out any details about your medical problems. We will ask you at each visit if this contact information has changed since your last visit so our records are up to date.

Be asked about treatments and medicines you are taking or have taken in the past and give research staff permission to review your medical records at the AIDS Center

Be asked about your mental health and drug use history.

Provide 4 tubes of blood to measure the level of HIV in your blood and how your liver, kidneys and other parts of your body are working.

Provide a urine sample to be tested for drugs such as heroin, amphetamines, benzodiazepines, and cocaine, and as another check on how your kidneys are working. If you are a woman, your urine will be tested to see if you are pregnant. You may not enroll in the study if you are pregnant because naltrexone is not approved for use during pregnancy.

These assessments will take about an hour. If they show that you meet study admission criteria, you will be scheduled to have the baseline assessment and then enter the relapse prevention phase.

Part 3 –BASELINE ASSESSMENT AND RELAPSE PREVENTION PHASE

This phase will last 48 weeks and includes:

An interview by research staff asking about your alcohol and drug use, employment, psychiatric symptoms, and legal and family social problems; questionnaires about how you are feeling; and another urine drug test and alcohol breath test.

You will be given a pill bottle with a special cap (called the MEMS cap – “medication electronic monitoring system”) that electronically records the time and date you open the bottle. This electronic record is a way that research staff will use to measure the degree to which you are taking ART medication exactly as prescribed. You and the research staff will choose one of your ART medications to put in the bottle that has the MEMS cap. IT IS VERY IMPORTANT THAT YOU KEEP THAT SPECIFIC MEDICATION IN THAT BOTTLE, AND OPEN IT ONLY WHEN YOU TAKE THE MEDICATION. IT IS ALSO VERY IMPORTANT THAT YOU BRING THE BOTTLE TO EACH COUNSELING SESSION SO RESEARCH STAFF CAN DOWNLOAD THE ELECTRONIC RECORD THAT SHOWS WHEN YOU OPENED THE BOTTLE.

Randomization into one of the two relapse prevention/treatment groups; this will be done by chance (like

the flip of a coin). One group will receive IN and placebo ON; the other will receive placebo IN and ON. Neither you, your doctor, or the treatment or research staff will know which group you are in. Only the study pharmacist will know, however your doctor can find out from the pharmacist if necessary in an emergency.

You will receive your first implant (IN or IN placebo) and a supply of ON or placebo ON after you are randomized so you have enough pills to last until the next counseling session. You are to take one pill each day and will receive a refill at the next counseling session.

After you receive an implant, you will come to the clinic 5-7 days later to have the implant site inspected for signs of irritation or infection and have the sutures removed. The implant site will also be checked at each counseling appointment and you will be referred for treatment if you are having problems at the implant site.

You will be scheduled for counseling every two weeks during the first 24 weeks and every month during the last 24 weeks at the addiction treatment center that is working with your HIV treatment program (Pavlov for Botkin Hospital; Leningrad Region Addiction Center for Leningrad AIDS Center). Counseling will focus on helping you avoid relapsing to heroin addiction, and helping you deal with problems that may have developed during your addiction or as a result of your HIV infection. The counselor will make sure that you get a new supply of ON or ON placebo so you have enough medication until the next appointment. Efforts will be made to schedule your study visits at times that are easy for you.

You will also meet with research staff every two weeks during the first 24 weeks and every month during the last 24 weeks to complete several assessments that will record how you are doing. The time taken to complete the assessments will vary from a half hour to 1.5 hours. They will always include a urine drug test and alcohol breath test; questions about drug and alcohol use; asking if you missed any doses of ART medication since the last visit and if so, how many; if you are having side effects from any of the medication and if so, what were they and how long they lasted; and if you had any treatment or received medication from anyone other than those at the AIDS Center or addiction program. Research staff will also download information from your MEMS cap as another way of measuring the degree to which you are taking ART medications as prescribed. It might be easiest for you to schedule these visits on the same day as the counseling visits.

Some assessments will require 1-2 tubes of blood to measure liver function, CD4 count and viral load.

If there is uncertainty about whether you relapsed since the last visit, a study physician may give you a naloxone test to make sure you are not addicted before giving you a refill of study medication.

You will receive a new implant at weeks 12, 24, and 36 unless you relapsed, and you will be examined very carefully before each implant to make sure you are not relapsed and are physically addicted to heroin or other opioids. Examination will consist of what you tell treatment and research staff about your drug use; looking for fresh puncture marks and signs or symptoms of withdrawal or intoxication; a urine drug screen that must be negative for opioids before you are implanted; information from friends or relatives if available; and a naloxone injection as a final test to make sure you are not physically dependent on heroin or other opioids before getting the implant.

If you have no contact with research staff for more than 45 consecutive days you will not be eligible to continue on study medication (IN/ON placebo; ON or IN placebo) but will be eligible to continue ART unless the doctors in the AIDS Center there think you should not continue. If you drop out of the naltrexone treatment, you will still be followed up at all scheduled assessment points unless you decline to participate.

This study will not provide naltrexone (IN or ON) after week 48. Most patients will probably benefit from continuing treatment and will be offered drug counseling at the addiction programs or referral to local health centers if they prefer. IN and ON will be available for those who can purchase it.

FOR WOMEN

The risks of naltrexone in pregnancy are not known and for that reason, naltrexone is not approved for use during pregnancy. Women must have a negative pregnancy test before receiving naltrexone and agree to use a medically effective method of birth control while on naltrexone. If you become pregnant during the study, the study medication will be stopped because continuing it may involve currently unforeseeable risks to you or to your baby.

You will have a urine pregnancy test before starting the study and be retested for pregnancy every 4 weeks through week 44 if you have continued on the study medication (IN or ON) to be sure you are not pregnant. Study medication will be stopped if you become pregnant. ART will be continued if you become pregnant unless the doctors at the AIDS Center think it should be stopped.

You must agree to use effective birth control while in the study. Examples are:

- Abstinence (not having sexual intercourse with anyone)
- Oral contraceptive (birth control pills)
- Norplant
- Depo-Provera
- Condom used with a spermicide (kills sperm)
- Cervical cap used with a spermicide (kills sperm)
- Diaphragm used with a spermicide (kills sperm)
- Intrauterine device
- Sterilization (having your tubes tied)

If you become pregnant will be asked to sign a release of information form to allow study staff to obtain information about the outcome of your pregnancy. Should you have any concerns, you may contact your obstetrician.

Will I be paid for being in this study?

There are 20 possible assessments (one every two weeks during the first 24 weeks and once a month during the last 24 weeks of the study) following the baseline assessment. You will be paid 500 roubles after completing 18 of these assessments and 1000 roubles for completing the assessments at week 24 and 1500 roubles for completing the assessments at week 48. No payments will be made for the baseline assessment.

What are the possible risks or discomforts?

The most common side effects of naltrexone are nausea, headache, dizziness, fatigue, insomnia, anxiety, and sleepiness. These are usually mild and of short duration. No serious long-term adverse effects have been detected among 600 or more adults who received naltrexone in previous studies done in St. Petersburg and the Leningrad Region Addiction Centers.

The most serious side effect of naltrexone is injury to your liver, which is most often associated with doses of 1400 to 2100 mg per week. These doses are much higher than the doses that will be used in this study. However, as a precaution we will do a blood test to measure your liver enzymes at the start of the study and at weeks 8, 16, 24, 36 and 48 while you are on the medication. If your liver enzymes are greater than 5 times normal at the baseline assessment, you will not be started on the study. If

you are on the study and any one of your enzymes increase to more than 5 times normal, the medication will be stopped. If you develop signs that may indicate liver damage such as fatigue, anorexia, jaundice, nausea, vomiting, dark urine, light stool, or abnormal stomach pain, you will be referred to a liver specialist for evaluation and a recommendation as to whether the study medication should be discontinued.

The naltrexone implant that will be used in this study was developed by ZAO Fidelity Capital in Moscow and is approved by the Committee of Pharmacology, Department of Health of the Russian Federation. The most common side effect of the implant is mild/moderate irritation lasting 2-3 days at the implant site.

Another risk is infection at the implant site. This has occurred in about 3% of the implants in a previous study done by the Pavlov and Leningrad research team. In all cases the infection was superficial and treated successfully with antibiotics. Precautions will be taken to minimize the risk of infection and include having a surgeon insert the implant using sterile disposable equipment in a room used only for phlebotomy and minor surgery with thorough cleaning of the site before and after the procedure. Some of the infections in the previous implant study may have occurred because patients tried to remove the implant. <u>We strongly advise that you not try to remove the implant after it is inserted. The implant will dissolve naturally in about 3 months. If you wish to have it removed, please make an appointment with the research staff to discuss the situation.</u>

Naltrexone administration will induce opioid withdrawal if a person is physically dependent on heroin or other opioids at the time he/she takes it. To avoid unintended withdrawal you will have a urine drug test, clinical evaluation, and a naloxone (Prodotone ™) test before starting the study. Naloxone is a medicine that will cause opioid withdrawal and its effects last for 30-45 minutes if you are physically dependent on heroin or other opioids. The naloxone test will be administered either intravenously or intramuscularly, and only if the other information you provide to the staff indicates that you are not physically dependent on heroin or other opioids. If you have withdrawal after the naloxone test, your symptoms will be treated with clonidine or a benzodiazepine and will go away in 45-60 minutes. You will not be started on the study until you pass a naloxone test, which means that you have no signs or symptoms of opioid withdrawal after naloxone is administered.

Patients who drop out of naltrexone treatment are at increased risk for overdose since they have lost tolerance to heroin and other opioids when they were detoxified before starting naltrexone. The potential for this problem is unavoidable since remission from addiction is a condition for starting ART. If you use heroin or other opioid drugs after stopping naltrexone, it is important to use doses much lower than those you used during the last time you were addicted.

Some of the questions about your personal habits, lifestyle and drug and alcohol use may be embarrassing or otherwise cause distress. These ratings include standardized assessments of drug and alcohol use, as well as assessments of psychiatric disorders including problems with mood, anxiety, anhedonia (lack of energy, feeling depressed) and hostility. Administration of all tests is supervised and conducted by trained research staff. All information is kept in locked files and protected by computer security measures so as to maintain confidentiality.

Drawing blood may cause pain, bleeding, bruising, lightheadedness, and, on rare occasions, infection at the site of the needle insertion. Using sterile equipment and cleaning the site with alcohol before the blood is to be drawn will minimize these risks. The total amount of blood that you will be asked to give during the study is about 24 tablespoons or 355 ml.

The study drug must be kept out of reach of children and anyone other than yourself.

Costs to you for participation

You do not have to pay for study medication, study visits, examinations or laboratory tests that are part of the study. You, the city, state, or your health insurance carrier will pay all other medical costs outside the study.

Circumstances where you might be asked to leave the study:

You may be asked to leave the study if a doctor in the AIDS Center or addiction treatment program feels that staying in it is harmful to you, or If your behavior threatens the integrity of the project, other patients, or staff.

You will also be asked to stop participating if the ethical committee at Pavlov, the University of Pennsylvania, or the study sponsor (U.S. National Institute on Drug Abuse) decides to stop or cancel the study

If you become incarcerated

If you miss a visit because you are incarcerated, your participation in the study will change. You will not receive any study medication while in prison. Also, depending on the length of time you are incarcerated, you may not be able to receive more study medication, even when you are released. Study staff will not try to contact you while you are incarcerated. However, we will, contact people you mentioned as a contact person to find out the date of your release.

Policy about research-related injuries

In the event of injury resulting from the research procedures, medical treatment in excess of that covered by third party providers will be provided without cost to you, but financial compensation for injury is not available.

Problems or questions

If you have questions about this study or in case of research related injuries, you should contact one of the investigators, Drs. Evgeny Krupitsky at (812) 296-9905, Edwin Zvartau at (812) 499-7023, or Dr. Dmitry Lioznov at (812) 499-7058. You may also contact your primary care physician or study physician at any time should you have a concern. In an emergency, call 112 and your study physician.

Crisis Intervention contact numbers for Medical and Psychiatric Emergencies are also available at: 296-9905 (Leningrad Regional Center of Addictions; and, 973-5396 (Pavlov State Medical University)

Your rights as a research subject

If you have questions about your rights as a research subject, you may call the Director in the Office of Research Administration of Pavlov Medical University at (812) 499-7166; or the Office of Regulatory Affairs at the University of Pennsylvania in the U.S. by calling 1-(215) 898-2614.

What if new information becomes available about the study?

Participation in this study may involve risks that are currently unforeseeable. You will be told if the investigators find out about new risks associated with naltrexone that are not currently known.

What are the possible benefits of the study?

You may or may not get a direct benefit from either of the treatments that are offered in this study.

However, it is possible that either of them will provide a chance to prevent you from relapsing to heroin and other opioid addiction, to keep the amount of HIV in your blood at a very low level and improve your HIV treatment outcome. If we find that one of the study medications works better than the other in keeping the HIV in your blood at a low level, the results could be helpful to other previously addicted patients who are at beginning ART and at risk for relapse to their previous addiction.

It is possible that the medical testing done in this study could reveal a medical condition that you were not aware of previously and for which you may need treatment. Study and clinic staff will refer you for additional treatment if such problems are identified.

Patients with a history of recent heroin addiction will receive a more integrated and pharmacologically effective relapse prevention treatment than they would normally receive. This combined approach may result in less relapse, better adherence, and better HIV treatment outcome over the length of the study. If results confirm our hypotheses, extended release naltrexone could become a treatment option to be used with patients who do not want agonist maintenance, or in settings where agonist treatments are unavailable or difficult to access. Such an approach could be helpful to thousands of opioid addicted patients in many countries who need treatment for HIV but are ineligible because they are active users or likely to relapse with its multiple unhealthy behaviors including poor ART adherence and increased risk of developing resistant

Your participation in this research is VOLUNTARY.

If you choose not to participate or are found not eligible to participate, your rights to health care or other services to which you are otherwise entitled will not be affected.

You have the right to drop out of the study at any time. If you decide to stop participation, you should notify the study doctors. Your previously collected study information will still be used and you will be given information about other treatment programs in your area so that you can apply for treatment elsewhere.

If you drop out or leave the study, we will contact you to obtain follow-up information on how you are doing, unless you instruct us not to do so. If you decide to withdraw consent for further participation, you will need to do so in writing.

If you fail to follow the study procedures or the study staff feels that it is in your best interest, the investigator may end your participation in the study. For example, you may experience an allergic reaction to the study medication and therefore would not be able to continue in the study. You will be given information about other treatment options.

Who can see or use my information? How will my personal information be protected?

The investigator and staff involved with the study will keep your personal health information that has been collected for the study strictly confidential. Staff and study monitors (people who look at the study to see if it is being done right) may review records that identify you.

The results of this research may be published in scientific journals or presented at medical meetings but

your identity will not be disclosed.

Consent to participate

When you sign this form, you are indicating that you agree to take part in this study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Upon signing below, you will receive a copy of this consent.

Your signature below also means that:

- You understand that taking part in this study is voluntary;
- You understand what the study is about and how and why it is being done;
- You understand the risks and possible benefits of the study;
- You have been told about other treatments that may be available to you;
- You understand that if you decide not to take part in this study, your refusal to participate will involve no penalty or loss of rights to health care or other services
- You understand that you can volunteer to take part in this study now and may withdraw at any time without penalty or loss of rights to health care or other services
- You understand that the results of this study may be published; however, you will not be identified by name or by any other personal identifiers;
- You understand your rights as a research participant;
- You understand that giving false, incomplete, or misleading information about your medical history, including past and present drug use, could have adverse consequences for your well being.

SIGNATURE OF PARTICIPANT

Name of Participant (printed)	Date	Signature of Participant

Name of Authorized Staff Member Obtaining Consent (printed)	Date	Signature of Authorized Staff Member

SIGNATURE OF INVESTIGATOR

I have explained the research to the participant and answered all of his/her questions. He/she has verbalized understanding of the information described in this document and freely consents to participat

Name of Investigator (printed)

Signature of Investigator Date

Appendix 3. List of ART medications

Combinations of ART Medication Used				NI	ON	Total
Protease inhibitor-based regimens						
Zidovudine	Lamivudine	Lopinavir/r		12	13	25
Lamivudine	Abacavir	Lopinavir/r		12	13	25
Lamivudine	Phosphazide	Lopinavir/r		5	3	8
Lamivudine	Stavudine	Lopinavir/r		2	2	4
Lamivudine	Didanosine	Lopinavir/r		0	1	1
Zidovudine	Lamivudine	Abacavir	Lopinavir/r	0	1	1
Zidovudine	Lamivudine	Atazanavir		5	6	11
Abacavir	Lamivudine	Atazanavir/r		6	4	10
Zidovudine	Lamivudine	Atazanavir/r		0	2	2
Lamivudine	Didanosine	Atazanavir		2	0	2
Lamivudine	Abacavir	Atazanavir		1	1	2
Zidovudine	Lamivudine	Darunavir/r		6	1	7
Lamivudine		Darunavir/r		3	3	6
Phosphazide		Darunavir/r		2	0	2
Stavudine		Darunavir/r		1	1	2
Zidovudine	Lamivudine	Fosamprenavir/r		0	3	3
Lamivudine		Fosamprenavir/r		2	0	2
Lamivudine		Saquinavir/r		0	2	2
Abacavir		Saquinavir		1	1	2
Zidovudine	Lamivudine	Saquinavir/r		0	1	1
Non-nucleoside reverse transcriptase inhibitor-based regimens						
Zidovudine	Lamivudine	Efavirenz		17	24	41
Lamivudine	Abacavir	Efavirenz		2	2	4
Lamivudine	Phosphazide	Efavirenz		3	1	4
Lamivudine		Efavirenz		0	3	3
Lamivudine	Didanosine	Efavirenz		1	1	2
Lamivudine	Stavudine	Efavirenz		1	1	2
Lamivudine	Zidovudine	Nevirapine		4	4	8
Integrase inhibitor-based regimens						
Lamivudine	Abacavir	Raltegravir		4	2	6
Zidovudine	Lamivudine	Raltegravir		1	3	4
Other Regimens						
Lamivudine	Efavirenz	Lopinavir/r		3	0	3
Lamivudine	Didanosine			2	0	2
Zidovudine	Lamivudine	Stavudine		1	0	1
Stavudine	Nevirapine	Efavirenz		1	1	2
				100	**100**	**200**

Table 4. ***List of ART medications***

Appendix 4. Post-hoc analysis of craving and clinical global impression of outcome.

Craving scores declined dramatically compared to baseline in naltrexone implant group throughout the study. In the oral naltrexone group the only significant differences compared to baseline were noted at weeks 6, 10, 14 and 16. Also, there were significant Main Group effect ($F_{1·167}$=5·28; p=0·0228) and Time-by-Group interaction ($F_{18·1863}$=2·12; p=0·0039; figure 4) which means naltrexone implant clearly demonstrated its anti-craving effect greater than oral formulation.

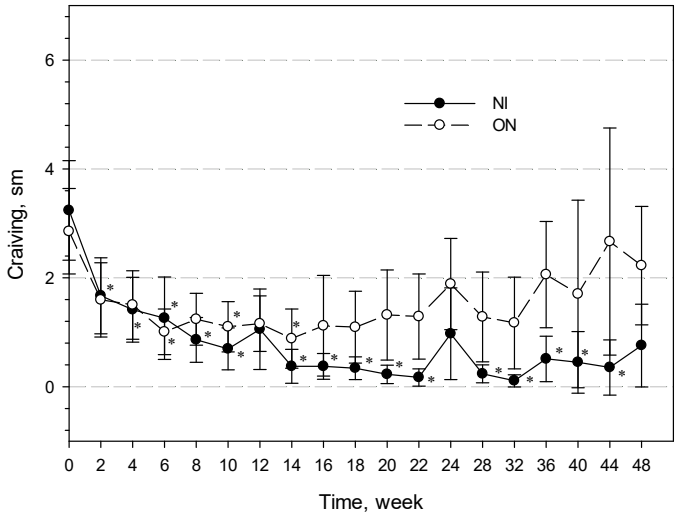

Figure 4: **Craving for opioids**

Statistical significance of differences between Craving for opioids at baseline and follow-up assessments (Mixed ANOVA Main Time effect. Tukey test for post hoc comparisons): *p<0·01. The means are the means for all patients with data at a given time point (Means with 95%CI).

The clinical global impression of outcome (CGI) showed more positive change in NI than ON (p=0·0029) with higher scores at week 48 in NI than ON (M±SD): 19·75±12·1 vs. 12·94±8·99 (p=0·0241).