Ask the expert: Q&A on the huntingtin-lowering trial program

In a Q&A coordinated by the UK HD Association, Dr Ed Wild answers questions on the recently-announced trial

By Dr Ed Wild December 18, 2017 Edited by Dr Jeff Carroll

The research news, announced on 11 December 2017, that a research team from the Huntington’s Disease Centre at University College London have made significant step towards a possible treatment for Huntington’s disease, raised many questions for the Huntington’s disease community. Dr Ed Wild answered some of these questions on behalf of the UK HD Association, helping to give some context to what this news means for people affected by Huntington’s now and in the future.

Ed says

Thank you for all your fantastic questions. It’s a testament to the dedication and determination of this community that there were so many thoughtful and detailed questions. I’ve answered as best as I can. While I am involved in the HTTRx program as an advisor and investigator, I am not speaking on behalf of Ionis, Roche or UCL here, but as a co-

founder of HDBuzz and scientific advisor to the HDA. None of my answers should be interpreted as medical advice. I hope you find them helpful!

> “First things first - the news that IONIS-HTTRx lowers the mutant huntingtin protein is great - but it is not a cure.”
> Image credit: Huntington Study Group

Could this modern medication cure somebody who already has Huntington’s? I’m aware that it will reduce the HD protein, but for those already suffering without medication is the damage already done? Or could clearing protein potentially help?

– Jodie

and

Will this help someone that has got HD or is it just for new sufferers?

– Mark

First things first - the news that IONIS-HTTRx lowers the mutant huntingtin protein is great - but it is not a cure. In general, I think it’s better to hope for an “effective treatment” because a cure is a VERY high bar to clear. We can’t cure HIV or diabetes, but medical advances have dramatically transformed those into manageable conditions. Progress happens gradually, and we need to be in this for the long haul.

That said, we do think that lowering the mutant huntingtin protein level with IONIS-HTTRx has the potential to make a positive difference, even after HD symptoms have begun. But we won’t know until a larger, longer trial has been run. In the trial that just finished, people were only treated for 3 months, which is too short a time to give any idea of whether the drug slows HD progression.

Throughout the course of HD, there are some neurons that have been lost, and others that are alive but unwell. We can’t replace lost neurons but we hope that the drug will enable the unwell ones to function better.

The earlier we treat, the more likely we are to see benefit. Unfortunately, even if we do see slowing or improvement in early HD, it’s likely that there will be a point later in the disease where the drug doesn’t produce significant benefits. Again, this is something we can only find out by testing it in more people for longer periods.

What are the next steps in using this treatment to make it available to other patients who are willing to try, as soon as possible. How and when?

– Arnar

and

Will it now be tested on a larger group of people? And if so, when is that planned?

– Steve

The next step is a longer, larger trial to test the drug’s “efficacy” - does it slow the progression of HD? That trial is now being planned and we expect an announcement from Roche in the coming months. If you have HD or are at risk, I have three pieces of advice:

1) Make sure you are under regular follow up at an HD clinic that has a research interest - either directly or at a site that can supply volunteers to other clinical trial sites.

2) Sign up for the ENROLL-HD study (details at enroll-hd.org). That study is used as a recruitment database for clinical trials and is the first place the teams will look once recruitment begins.

3) Look after yourself. The next trial may be over a year away, and the healthier you are, the better the chance of being in the next trial. Keep up with clinic visits, GP visits, psychiatrist visits, physio, speech and language therapy.

Stay active, exercise and eat well. Seek advice early if your HD is taking a turn for the worse, or if any new medical problems arise. Sign up for HDBuzz email alerts – hdbuzz.net.

When do you think the drug will be available to people who have tested positive or are showing symptoms?

– Sophie

and

What is the criteria to become part of the trial, and how many sufferers will be in the new intake?

– Maria

My best guess is that the next big trial will begin in late 2018 or early 2019. That sounds a long way away but setting up a trial with perhaps dozens of sites and hundreds of patients is a huge thing to organise. Roche, Ionis and the academic researchers are all working as fast as possible to get the next steps planned.

I think we can expect that trial to last around 3-4 years start to finish. Again that sounds like a long time, but that is how long will be needed to give the drug the best chance of showing that it works. The worst case scenario would be to rush the next trial and get a negative result because the trial was too short.

On the flip side, if the drug turns out better than we hope, the trial might be shorter.

If the result is good, Roche will apply for a licence to prescribe it, which could push the total time to 5-6 years or even longer if there are snags along the way. It's worth being honest here and confessing that scientists generally UNDERestimate how long these things take. I'm sorry if it takes longer than the guesses I've given here. If it does, it won't be because we aren't trying 100%.

Finally, it's worth pointing out that it's possible the trial will show that the drug doesn't work - that it doesn't slow the progression of HD. That would be bad news, and we would have to figure out why it happened and see what we can do about it - but it wouldn't take away the fact that the gene and the protein are the best target for fighting HD.

Curious about effectiveness in JHD.

– Tyler

The current trial had a minimum age of 25, so no JHD patients were enrolled. The same protein is responsible for JHD, so if the drug works for later-onset HD, it should work in JHD too. However, JHD is a more aggressive form of the disease, and the brain of young people might be more sensitive to side-effects, so it might be harder to treat even if the drug works well. I can promise you that finding out answers to these questions and helping people with JHD is a top priority for everyone involved.

Are the patients who were on the trial continuing with the treatment?

– Laura

Yes. The 46 volunteers in the trial that just finished will be invited to participate in an 'open-label extension' study or OLE. All OLE participants will regularly receive the active drug - none will be given a placebo. There are three reasons for this.

1) To thank them for taking the risk of being among the first humans to receive this drug. Everyone who takes part in HD research is a hero helping to change the world, but these 46 have taken perhaps the biggest personal risk on behalf of our community.

2) To get more data, as soon as possible, about longer-term safety of the drug.

3) Because people usually cannot be in 2 different stages of the same program - so these 46 people probably wouldn't be allowed to take part in the next trial phase.

> **"**The next step is a longer, larger trial to test the drug's "efficacy" - does it slow the progression of HD? ″

I think many people don't get tested as so far there isn't much you

can do if you have a positive result. If you choose not to get tested before this starts will it effect how quickly you can have the treatment?

– Ruby

Getting tested is an intensely personal decision and I would not want to sway or persuade anyone either way. It is something to be considered bearing in mind all the pros and cons, in discussion with loved ones and your genetic counsellor.

The next big trial will almost certainly involve people who have signs and symptoms of HD, and who have had a positive genetic test. But the one after that may well look into people with a positive genetic test result and no symptoms yet, to see whether it prevents the disease. It's likely that people will need to know their genetic status to take part in that prevention trial. I don't know how far away that trial is, because it depends so much on how the next trial goes.

This week's announcement isn't a reason to get tested . When prevention trials are announced, and if they require testing before you can take part, there will still be time to get counselling and get tested if that is what you want to do.

On the upside, there's one thing you can do now, to help with HD research AND get your name on the list of people interested in future trials, even if you HAVEN'T been tested. That's to sign up for Enroll-HD (http://enroll-hd.org). At-risk, untested HD family members can take part.

At what stage of disease progression can the drug be given? i.e. Can it be given prior to symptoms showing therefore acting more as a preventative measure? From my understanding (please correct me if I've misunderstood), as the protein builds up in the brain symptoms progress - will the drug be effective if there is no build up present?

– Nicky

We expect the next trial to be in people with early HD, but work is already underway to think about trials to test whether it can prevent onset in people without symptoms. That is definitely the goal. We don't know how early it might be effective or might need to be taken but I think we may be able to use the protein concentration in spinal fluid, and other measures (biomarkers) in the future to guide treatments. But first it all needs to be examined in clinical trials.

I understand that this trial has established the safety of the drug and an initial indication that it may be effective. Will the next stage look at persistence within the body to start looking at what sort of drug regime may be necessary? For example, a lumbar puncture once a year to inject the drug is probably acceptable, a weekly one probably not!

– David

Everyone involved wants to come up with a regime that's effective but has the fewest possible number of lumbar punctures. I expect different options to be tested in future trials, but we don't yet know what those options might be.

I'm interested to know what are the next stages of clinical trials, and provided it is validated at each stage what are the optimistic and conservative estimates on when the treatment would be on the market? Also, will it be available earlier under Expanded Access/Compassionate Use?

– Jennifer

IF HTTRx genuinely DOES slow the progression of HD, I think for being able to prescribe the drug through the NHS, my optimistic estimate would be 5-6 years, very conservative estimate 10-12 years. Others might give you more or less optimistic numbers! And if we get a negative or disappointing trial result along the way, things could change dramatically.

But remember - HTTRx is not the only drug in development for HD - it's just the one we're most excited about. There are many ways of achieving the goal of lowering mutant huntingtin, expected to start new trials soon or already in early trials. Plus, there are other drugs being developed and tested that aim to slow or prevent HD in other ways, by helping restore normal functioning of the brain in the presence of the mutant huntingtin protein.

I think it's too early to speculate about expanded access or compassionate use - first we need to figure out whether the drug works and if so, try to get it licensed as quickly as possible.

Will the trials still be London based or will you be involving other research centres yet?

– Michela

No information about trial centres has been announced yet - except that the next trial is expected to involve sites in the USA. But I expect it to be a multi-national study and of course I am enthusiastic for London and other UK sites to be involved.

I recently joined Enroll-HD a few weeks ago. If/when this new gene treatment becomes available, must one have the blood test to determine one's CAG? Or if one's blood was taken as an Enroll-HD patient will that suffice, if it is determined that they are positive for the mutation, or must they have a separate blood test done?

– Gabby

Your Enroll-HD blood test result will never be revealed to you or to your Enroll site. Only a clinical test result given to you after genetic counselling could be used to decide whether you are eligible for future prevention trials. See my answer to Ruby on what this week's announcement means for testing decisions. (Long story short - don't get tested on the basis of this announcement!)

Would it be possible for a person to volunteer to be on this amazing drug trial if they are in later stage of Huntington's, as my husband is?

– Joyce

Civil Rights activist Fannie Lou Hamer said "Nobody's free until everybody's free". All of us working on HD want treatments that work for everyone, and won't stop trying until HD is no longer a problem in anybody's life.

But the harsh reality is that even if HTTRx were perfectly effective, it would never be able to restore brain cells that have already been lost.

We want to test the drug in as broad a spectrum as we can, and we may be pleasantly surprised . But the next big trial is likely to focus on people with relatively early HD symptoms, so that it has the best chance of showing slowed progression.

However hard we all try, inevitably, I'm afraid there will be some people for whom progress comes too late, and I'm sorry to you, your husband and anyone else if we don't get there in time.

My brother is on the trial database. Will he be receiving this treatment?

– Leanne

Being on a database of interested potential research volunteers is a great step, but there is no way to guarantee participation in any future clinical trial. At the moment we don't even know where the next trial will be running, or

what kind of patients will be eligible. I suggest you give your brother my 3 bits of advice above to maximise the chances. If he cannot be in the next trial of this drug, he should consider taking part in other trials and research studies – all are important for making progress as quickly as possible.

Will the treatment be cheap enough for everyone to have access to the treatment without restrictions because of costs to the NHS?

– Dawn

It's too early to have any clear idea about cost so I can only answer in general terms. Developing and testing new drugs, especially advanced therapies like HTTRx, is very expensive - but on the flip side, managing Huntington's disease throughout its course is already very expensive in terms of care and lost revenue. It wouldn't make any sense for a company to develop a drug that nobody can afford - that's bad business. My amateur prediction is that we can expect a significant price tag followed by a negotiation between healthcare purchasers and NICE that leads to the drug being made available. We may need to work together to ensure it's made clear to the decision-makers what the unmet need is in HD - but that's a problem for when we know whether the drug actually works to slow progression.

Is this treatment effective in people with spinocerebellar Ataxia type 17 (Huntington's like 4)?

– Elaine

IONIS-HTTRx only reduces the huntingtin protein, so it would not work for SCA17 I'm afraid. Though the two diseases look alike, they are caused by completely different proteins. The new family of drugs to which HTTRx belongs, called ASO drugs, can theoretically be designed to target any protein, so it's possible that a future programme might involve SCA17.

Ed is an investigator and advisor to Ionis and Roche on the HTTRx program, but is not answering on their behalf here.
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- Glossary
- **spinocerebellar ataxia** A family of diseases which result in characteristic movement disorders. Many types of spinocerebellar ataxia are caused by the same type of mutation as HD – a CAG expansion.
- **huntingtin protein** The protein produced by the HD gene.
- **clinical trial** Very carefully planned experiments designed to answer specific questions about how a drug affects human beings
- **efficacy** A measure of whether a treatment works or not
- **neuron** Brain cells that store and transmit information
- **placebo** A placebo is a dummy medicine containing no active ingredients. The placebo effect is a psychological effect that causes people to feel better even if they're taking a pill that doesn't work.
- **ASOs** A type of gene silencing treatment in which specially designed DNA molecules are used to switch off a gene
- **juvenile HD** Huntington's disease where symptoms begin before the age of 20.
- Read more definitions in the glossary

For the global HD community.

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