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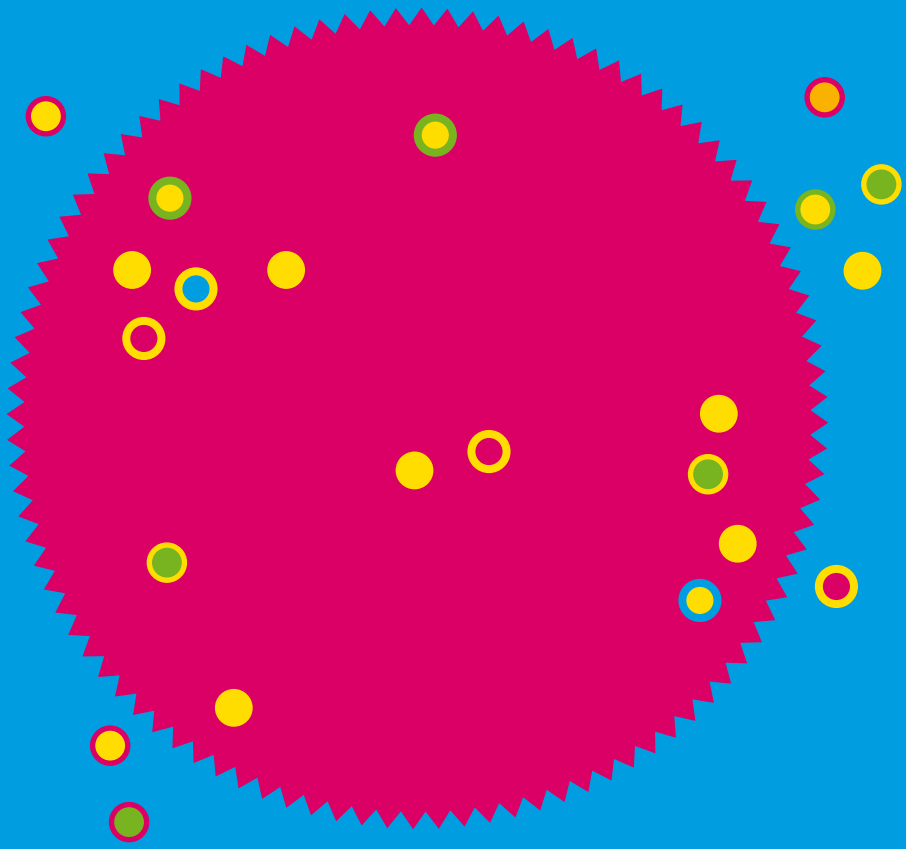
Guide to changing ART:

what to do if viral load rebounds

December 2017



HIV i-Base
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Watch for out-of-date information

Viral blips and viral rebound
Why adherence is so important
Resistance testing
New research

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Written and edited by Simon Collins for HIV i-Base. Thanks to the advisory group of HIV positive people and healthcare professionals for comments and to Monument Trust for funding this publication.

Disclaimer

Information in this booklet is not intended to replace information from your doctor.

Treatment decisions should always be made in consultation with your doctor.

This booklet is about changing your HIV treatment. It includes:

- When you might need to change treatment and why.
- Which tests are used and what the results mean.
- How to choose your next meds.
- How to make sure the next treatment will work.

It includes information about:

- Drug resistance, and
- New drugs and other research.

Summary

1. If your viral load becomes detectable it is important to take this seriously.
2. It may just be a lab error, so repeat the test to check.

   Do this when you get the first result. Don't just wait until your next routiine test.
3. Often, the second test will be back to undetectable. This may just have been a blip.
4. If the second test is still detectable, talk to your doctor about the cause. Is it due to adherence, drug resistance, drug absorption, or a combination of reasons?
5. A resistance test will help decide what to do next.

   The results need to be interpreted by an expert.
6. If you have to change meds it is usually best to use drugs that you have not used before.
7. If adherence was a problem, you might need extra support. This is so that the next meds don't fail too.
8. Test your viral load within 2–4 weeks to check the new meds are working. Test every month until your viral load is undetectable. Talk to your doctor if you have problems with adherence or side effects.
9. Ask about ongoing research. Find out whether new meds are likely to be available and when.
10. Don't rush to use one new drug if it is the only drug that will be active. Always try to use at least two new drugs in the next combination.
11. If you are waiting for new meds it is still good to be on treatment. Your options will depend on your current health and CD4 count.
12. Use drugs that are still active and that are less likely to develop resistance. Check that your doctor is talking to other experts about your care.

Introduction

This booklet is about changing HIV treatment due to drug resistance.

This updated edition only needed minor changes. HIV treatment in the UK is now very effective.

- Most people starting treatment get an undetectable viral load with their first HIV combination. Only about 1 in 20 people (5%) need to change because viral load does not reach undetectable.
- Also, less than 1 in 20 people (5%) who are on stable treatment need to change their meds each year due to resistance.
- In 2017, most people on their second or third combination still have new drugs to use that will work.
- Only a few people have resistance to all or nearly all drugs. In this case, information about new drugs is essential.

This booklet includes information on all these different situations.

The information is based on UK and European treatment guidelines.

www.i-base.info/treatment-guidelines

Changes to this edition

The changes to this edition are mainly minor.

The most important changes are about new drugs and ongoing research.

Other booklets in this series

• Introduction to ART

• HIV and quality of life: guide to side effects and long-term health

See page 22 for details.

Reasons to change meds

There are two main times to change your treatment.

1) If your viral load never becomes undetectable. See page 7.
2) If your viral load was undetectable but starts to rise again (viral rebound). See page 8.

In both cases your treatment could have failed.

This booklet is about these two situations.

A third reason to change is if you have side effects.

It is always important to talk to your doctor about side effects. Changing treatment is usually easy. It can really improve your quality of life.

A separate booklet is available if you are changing because of side effects.

www.i-base.info/guides/side

Why is viral load important?

A viral load test checks how well your treatment is working. When you are on treatment this test is often more useful than your CD4 count.

A viral load test shows whether the drugs are working when you first start treatment.

It shows whether your meds are still working when you are stable on treatment.

How accurate are viral load tests?

In the UK, viral load tests have a cut-off of 20, 40 or 50 copies/mL. Below this level, viral load is called undetectable.

The differences between these tests are not significant.

It is common for viral load to be less than 5 copies/mL

However, viral load tests have “a three-fold margin of error”.

This means that a result of 50 could really be anywhere between 16 (3-fold lower) and 150 (3-fold higher). A result of 500 could be anywhere between 50 and 1500.

This is why it is essential to confirm an unexpected result.

If your viral load never became undetectable

How quickly should viral load become undetectable?

When you first start treatment, viral load drops quickly.

Many people become undetectable within the first month and most within three months. Some people take longer.

The time it takes to become to undetectable depends on several things:

- Your viral load when you start. The higher it is, the longer it will take.
- Which HIV drugs you use. Integrase inhibitors reduce viral load faster than other meds.
- Adherence. Drugs can only work if you take them. If you take your meds on time, viral load comes down more quickly.

Viral load should drop by at least 90% in the first month. If not, your doctor will ask you about adherence and may take other tests.

If viral load is still detectable after 3-6 months, it is normal to change treatment.

What is second-line treatment?

Second-line is the name for your second combination.

If this second treatment fails, your next treatment is called third-line.

How long should I wait before changing?

This will depend on your individual situation.

It will depend on why treatment might not be working and on the results of other tests.

What to do if viral load rebounds

Getting a second test

A low-level rebound might only be a lab or test error.

It might just be a small blip that goes back down again.

This is why it is important to repeat the test.

The second test should be taken when you get the detectable result.

Don't just wait for weeks or months until your next routine test.

If the second test is still detectable this is a "confirmed viral rebound".

Viral load blips

Viral load blips are common.

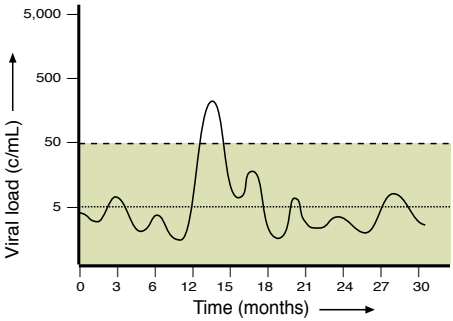
A blip is when viral load goes above 50 for a short time and then drops back down. See Figure 1.

Most blips are not detected because viral load is only tested once or twice a year.

Blips can be defined as an increase from less than 50 to 200, 500 or even 1000. Most blips are under 200. Blips can be caused by other infections, such as flu or herpes, or a recent vaccination.

Some blips are just lab errors.

Figure 1. Viral load blip



A single blip above 50 is common. It doesn't mean you need to change treatment.

A blip is usually undetectable again on the confirmatory test.

Confirmed viral rebound

If the second test shows your viral load is detectable at a similar or higher level – and you have been taking your meds – this confirms viral rebound. See Figure 2.

It is likely you have started to develop resistance to some or all of the drugs in your combination.

Most guidelines recommend changing treatment.

This is because HIV can develop resistance even when viral load is relatively low (between 50 – 500).

How can drugs "fail" when I feel fine?

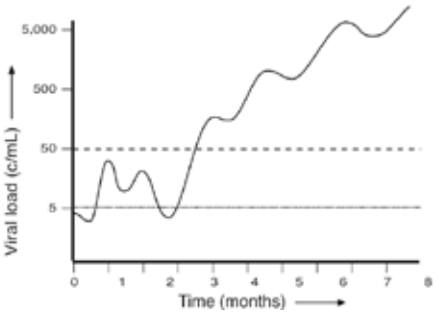
Viral failure relates to results from a blood test but not to how well you feel.

But, if you stay on a failing treatment, your CD4 count will start to drop.

This might not be for several months but it will happen.

A lower CD4 count increases the risk of new or progressing illness. This is called **clinical failure**. See Figure 3.

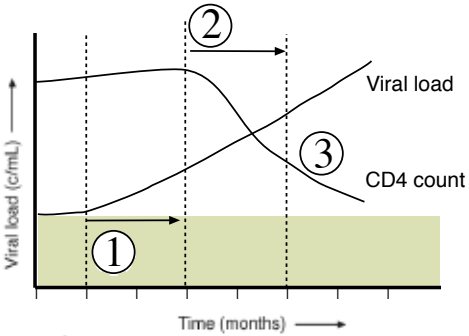
Figure 2. Viral load rebound



If the second viral load test is still detectable, and the person has been taking their meds, this is more likely to be a real rebound.

This can be a reason to change treatment.

Figure 3. From rebound to symptoms



① *Viral load rebounds. If you stay on the same meds, viral load will continue to rise.*

② *Your CD4 count will go down over time.*

③ *As your CD4 count drops the risk of symptoms increases. This becomes clinical failure.*

Reasons a combination can fail

If your viral load rebounds it is important to find out why.

This is to help make sure the next combination will work better. Your doctor will need your help to decide which of the reasons below are most important to consider.

There are more than 30 HIV drugs and formulations. However, there are only a limited number of combinations.

This is because resistance to one drug can limit the use of other drugs that are similar.

Reasons a combination can fail		What to do about it
1) Information.	Maybe you did not have enough information or support to understand how to get the best from your meds.	Take control of your own health. Ask questions about treatment until you are happy with the answers. Talk to your doctor, health advisors and friends. Read leaflets and websites. Ask for help.
2) Adherence. If you missed or were late with your meds.	Your doctor is likely to talk about adherence first.	Be as honest as you can. If you did not miss doses it is important that your doctor believes you. See page 13 for tips.
3) Taking meds with or without food.	Some drugs need to be taken with food and others without food to reach the right levels.	Check that you had the right information. Not following this advice might mean you were only getting half the dose.
4) Low drug levels.	Some people absorb low drug levels. This is less common with modern meds but may still be worth checking.	Drug levels can be checked for most drugs except NRTIs ("nukes").

Reasons a combination can fail		What to do about it
5) Drug resistance before treatment.	Resistance might have been missed before you started. Even taking all your meds on time can't overcome drug resistance.	Get a new resistance test and an expert review of previous tests. This will help choose your next drugs.
6) If your combination had side effects.	No matter how good your combination is, you have to be able to take it, if you have difficult side effects, or it is too difficult to take, then ask if there are other options.	Use new drugs that are still likely to be active. If side effects were a reason for missing doses, it is important that your doctor knows this. There are likely to be other meds you can use.
7) Drug interactions may have reduced the drug levels of your HIV drugs.	Other medications or supplements can interact with HIV drugs. This includes meds you can buy over the counter without a prescription. It can include vitamins and minerals and some recreational drugs.	Your HIV doctor and pharmacist need to know about all your drugs and supplements. This is to check for potential interactions. See: www.hiv-druginteractions.org
8) The drugs in your last combinations.	Some drugs are not recommended at high viral loads.	Check that the drugs in your last combination were right for your viral load.

Why adherence is linked to drug resistance

The doses of HIV drugs are worked out to give you effective drug levels for 24 hours a day.

These levels should be high enough to be active and not get resistance. They should not be so high that they cause side effects. See Figure 4.

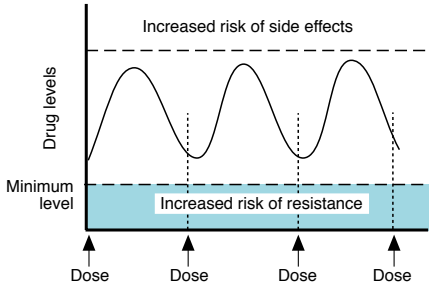
But HIV drugs can only work if you take them.

Missing doses or being late taking your meds increases the chance of drug resistance. See Figure 5.

Drug resistance will stop treatment working. Resistance changes your virus forever. It reduces your choice of drugs.

This can affect current meds and new drugs in the future.

Figure 4: Drug levels with good adherence

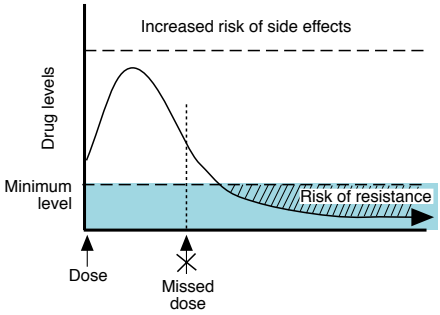


Drug doses are worked out to cover the whole dose period.

Levels need to be high enough to be active against HIV without risking resistance.

Levels need to be low enough to minimise the risk of side effects.

Figure 5: A missed or late dose increases the risk of resistance



Missing doses or being late taking your meds lets the drug levels fall below the minimum level needed. Drug resistance can then develop.

The more often you are late or miss a dose, the greater the chance that resistance will occur.

What if I forget?

Almost everyone will forget or be late with their drugs at some time. If this happens you will still be okay.

But there is a difference though between occasionally missing a dose and regularly forgetting on a daily or weekly basis.

- Each time you miss or are late there is a chance that resistance can develop.
- Be honest when looking at your adherence.
- If your adherence is not good, your doctor can help but you need to talk about it. Support is available but you will need to ask.

Adherence tips

The following tips are from the i-Base Introduction to ART.

Some drugs have more flexibility with timing.

Remember that recommendations to take with or without food are important.

- Find out what is involved. How many pills? How often? How exact is timing?
- Use a daily or weekly pill box. You can see if you miss a dose.
- Use the timetable on page 14. Mark off each dose and the time that you take it.
- Talk to your doctor if you have trouble.
- Set up an alarm using your mobile phone or watch.
- Take extra meds if you travel in case flights change.
- Keep an emergency supply.
- Ask a friend to help you remember.
- Ask friends if they have ideas that can help.

For more tips.

www.i-base.info/guides/starting/adherence-tips

Adherence diary

Use the table below to mark the time you take each drug. Take this with you when you see your doctor.

It will help you record if you are late or miss a dose.

Good adherence will help protect your new combination.

Week beginning: _____

	Drug names	Time (AM)	Drug names	Time (PM)
Monday				
Tuesday				
Wednesday				
Thursday				
Friday				
Saturday				
Sunday				

Other monitoring tests

The following tests are also used when changing treatment.

See online links for more details.

Resistance tests

Resistance tests can show whether HIV is resistant to HIV drugs that you are taking. The test doesn't always tell you about other drugs you have taken in the past.

Drug resistance involves changes to the structure of HIV that are called mutations.

For example, the mutation called M184V will stop 3TC and FTC from working. It reduces abacavir from being fully active.

The mutation K103N stops efavirenz and nevirapine from working.

Other mutations can be more difficult to interpret.

The i-Base website has more information about resistance tests and how to understand the results.

www.i-base.info/guides/changing/resistance-tests

The website also includes an online course that explains drug resistance in greater detail.

www.i-Base.info/ hiv-and-drug-resistance

See page 20 to record your results.

Drug level tests

Drug level tests are also called TDM (for Therapeutic Drug Monitoring).

TDM can check whether your body is absorbing the right drug levels.

www.i-base.info/guides/changing/tdm

Viral tropism

This is a type or resistance test to see whether you can use a drug called maraviroc.

www.i-base.info/guides/changing/viral-tropism

Getting the tests in the UK

Many hospitals routinely use all these tests when they are recommended in UK treatment guidelines.

Sometimes you may have to ask to know the results. Each test is important in different situations.

If your doctor says they are not available due to cost, write to your clinic and don't accept no for an answer.

Patient demand can be effective.

Please call the i-Base phoneline if you want information about this.

When should I change and which drugs can I use?

If viral rebound is confirmed, changing your combination will reduce the risk of further resistance.

With some drug classes, switching early might mean you can still use other drugs in the class. This is especially important for NNRTIs, integrase inhibitors and T-20.

Each situation will be different. The timing for when you change will depend on how high viral load has rebounded.

It will also depend on the reasons for the rebound.

Some people change treatment if their viral load stays consistently detectable above 50 copies/mL.

Other people wait until viral load is confirmed above 200 or 500 copies/mL in case this is still a blip.

A resistance test can help decide.

Anyone with drug resistance needs to consider their treatment history before choosing the next meds.

- Usually you will have to change all your drugs.
- Sometimes you can just change one or two drugs.
- Sometimes you can just add one drug to intensify treatment. This is not generally recommended.

How do I choose new drugs?

If you are changing treatment the choice of new drugs depends on:

- Your previous treatment history. This includes the meds you have already used and whether you developed resistance to them.
- Your current CD4 count and lowest ever CD4 count (called CD4 nadir).
- Your general health.

When choosing a new combination, you and your doctor will want to pick drugs that are most likely to work.

This will include looking at study results for new drugs.

It will include avoiding drugs with cross-resistance.

Cross-resistance is when resistance to a drug you have used means you are also resistant to similar drugs that you have not used.

Cross-resistance is common for all types of HIV drugs.

Cross-resistance is complicated. This is why your care needs to be managed by a doctor who is an expert in drug resistance.

General ideas or principles

Three general ideas increase the chance of your next treatment working.

1) Using drugs from a new class.
2) Using drugs from classes you have used before but did not develop resistance to.
3) Using more, rather than fewer drugs.

Treatment guidelines also outline ways to choose new drugs.

www.bhiva.org

Your new combination will depend on your HIV drug history.

It will also depend on the reason that your previous combination failed (see pages 10—11) and on the results of other tests (see page 15).

Resistance tests will help pick meds that may work, even when you have some resistance.

Cross-resistance by drug class

NRTIs

Cross-resistance between NRTIs is complex. Some drugs are active even with some resistance.

NNRTIs

There is strong cross-resistance between some NNRTIs. But, etravirine can work against other NNRTI resistance.

Protease inhibitors (PIs)

There is strong cross-resistance between some PIs. Some PIs, including darunavir/r and tipranavir/r, can work against early PI resistance.

Integrase inhibitors

As a new class, integrase inhibitors work if you have resistance to other drug classes. But they can also have cross-resistance within the class.

Resistance to raltegravir or elvitegravir can sometimes be overcome with high-dose dolutegravir.

Information on each HIV drug:

www.i-base.info/guides/category/arvs

When to use new drugs and when to wait?

Any new combination should use at least two, and preferably three, active drugs.

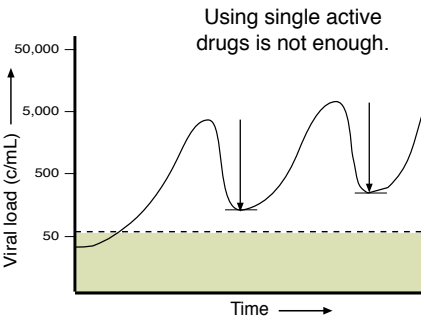
But, using new drugs without other meds that are active will only give a short-term benefit. Viral load is likely to rebound again with more resistance. See Figure 6.

It is only worth using one new drug if your CD4 count is very low (less than 50 cells/mm^3) or if you have other serious symptoms.

Waiting until you can use at least 2–3 new drugs together at the same time is usually a better strategy.

It will make the new combination stronger. It will then perhaps be able to reduce viral load to undetectable, when the benefit will be long term. See Figure 7.

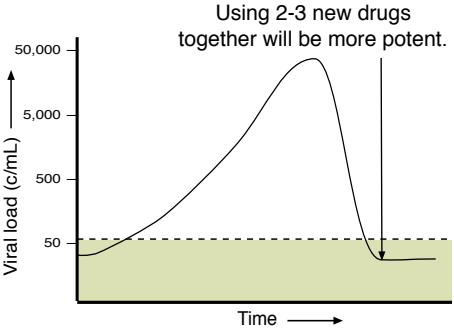
Figure 6. Using only one active drug will only work for a short time



Only one active drug is unlikely to get viral load to less than 50 copies/mL.

If a new drug is not helped by other active drugs, new resistance will develop ecah time.

Figure 7. Waiting to use three new drugs may get viral load undetectable



Waiting to use two or three new drugs together will make the new combination stronger. Viral load can now get to less than 50 copies/mL.

If viral load gets to below 50 it is likely to stay there without rebounding or developing further resistance.

Pipeline drugs, expanded access & non-ARVs

New drugs are being developed in existing and new drug classes.

Learning about upcoming reseach can help you plan when to change and when to wait. This might include studies that you could join.

The i-Base website includes a pipeline report on new drugs in development.

http://i-base.info/pipeline-2017

This includes the following new compounds, although not all these drugs will work against drug resistance.

NRTI: EFdA, GS-9131.

NNRTI: doravirine, elsufavirine.

Integrase inhibitor: cabotegravir (similar to dolutegravir) and bictegravir.

Attachment inhibitor: fostemsavir. combinectin.

Fusions inhibitor: albuvirtide.

Monoclonal antibody (mAbs): ibalizumab, UB-421, PRO-140.

Additional drugs might become available before this booklet is next updated.

Expanded access drugs

Some new drugs are available before they are approved for use in the UK. This is called an Expanded Access Programme (EAP) or a Named Patient Programme (NPP).

These drugs can be the key to your next combination. You will also be monitored very carefully for side effects and to check they are working.

You may need to register at another clinic to access EAP drugs. Your doctor can help you do this.

Get to know which drugs are in the pipeline and ask your doctor to give you the choice to use them.

Non-ARV drugs & other strategies

Some people may benefit from non-HIV drugs that are still active against HIV, e.g. peg-interferon or aciclovir.

These drugs can be prescribed on a named patient basis.

See these links for other drugs and strategies.

www.i-base.info/guides/changing/non-arv-drugs

www.i-base.info/guides/changing/other-treatment-strategies

Resistance test results

Date	Results (use separate pages if needed)

Further information

If you have questions after reading this guide contact the i-Base information service by phone or email.

0808 800 6013

questions@i-Base.org.uk

The EMA website includes patient information on all HIV meds in most EU languages. It also includes the full prescribing information.

www.ema.europa.eu

The following community sites include information on new drugs, and include updated reports from HIV conferences.

www.i-Base.info

www.aidsinfonet.org

www.natap.org

www.aidsmap.com

www.tpan.com

Feedback

Your comments help us improve these guides and are appreciated.

Comment online: www.surveymonkey.com/s/MK9R928

Or post free to: FREEPOST RSJY-BALK-HGYT,
i-Base, 107 The Maltings, 169 Tower Bridge Road,
London SE1 3LJ.

1. How easy was the information in this guide to understand?

☐ Too easy ☐ Easy ☐ Difficult ☐ Too difficult

2. How much of the information did you already know?

☐ None ☐ A little ☐ Most ☐ All

3. Will the guide help you be more confident when speaking to your doctor?

☐ Yes, a lot ☐ Yes, a little ☐ Maybe ☐ No

4. What did you find most useful?

5. Do you still have questions after reading this guide? Please include a contact email address if you would like us to reply to you.

6. Other comments?

Contact details (if you would like a reply): Name _____

Email _____ @ _____

i-base
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Other publications

All publications are free.

Please photocopy or post this form to

HIV i-Base, 107 The Maltings,

169 Tower Bridge Road,

London SE1 3LJ.

or fax to 020 8616 1250 or order online www.i-Base.info

Please also give us feedback using the form on page 21.
Answers will remain anonymous.

Treatment guides are written in everyday language.

HIV Treatment Bulletin (HTB) uses more technical language.

Please send me

Introduction to ART ..... ☐

Guide to hepatitis C for people living with HIV ..... ☐

HIV, pregnancy and women's health ..... ☐

HIV and quality of life: guide to side effects ..... ☐

Guide to HIV testing and risk of sexual transmission ..... ☐

Treatment passport (to record your treatment history) ..... ☐

ART in pictures: HIV treatment explained ..... ☐

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Glossary

ART: antiretroviral treatment.

ARV: antiretroviral - an HIV drug.

CCR5 inhibitor: an HIV drug that blocks HIV from attaching to a CD4 cell (eg maraviroc).

confirmatory test: a second test to double-check the results of a previous one.

cross-resistance: when resistance to one drug causes resistance to a different but similar drug.

expanded access: a way to use a drug access before it is fully approved. This is for people who need them urgently. It is also called "early access" or "named-patient".

genotype: relating to the genetic structure of an organism.

integrase inhibitor: a type of HIV drug that stops HIV from linking into the DNA in a cell (eg raltegravir, elvitegravir and dolutegravir).

mutation: a change in the structure of HIV that can stop a drug working.

NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor, a type of HIV drug (eg nevirapine, efavirenz, etravirine and rilpivirine).

NRTI or **'nuke'**: Nucleoside Reverse Transcriptase Inhibitors (also called nucleoside analogues) are a type of HIV drug. This includes AZT, d4T, 3TC, FTC, ddI and abacavir. Tenofovir (TDF or TAF) is a nucleo*tide* RTI and works in a similar way.

PI: protease inhibitor - a type of HIV drug that includes indinavir, nelfinavir, ritonavir, saquinavir, fosamprenavir, atazanavir, lopinavir, tipranavir and darunavir.

second-line therapy: the combination used after your first treatment has failed.

treatment-experienced: someone who has already used ART.

treatment-naive: someone who has never taken HIV treatment before. *People who are treatment naive can still be resistant to HIV drugs if they were infected with drug resistant HIV.*

viral tropism: the type of co-receptor used by HIV in order to attach (and then infect) a cell. HIV can use CCR5 (R5 tropic), CXCR4 (R4 tropic), or both (dual or mixed tropic).

viral load test: a blood test to measure the amount of HIV in your blood. Each test has a cut-off (usually 50 copies/mL). Results below this cut-off are called undetectable.

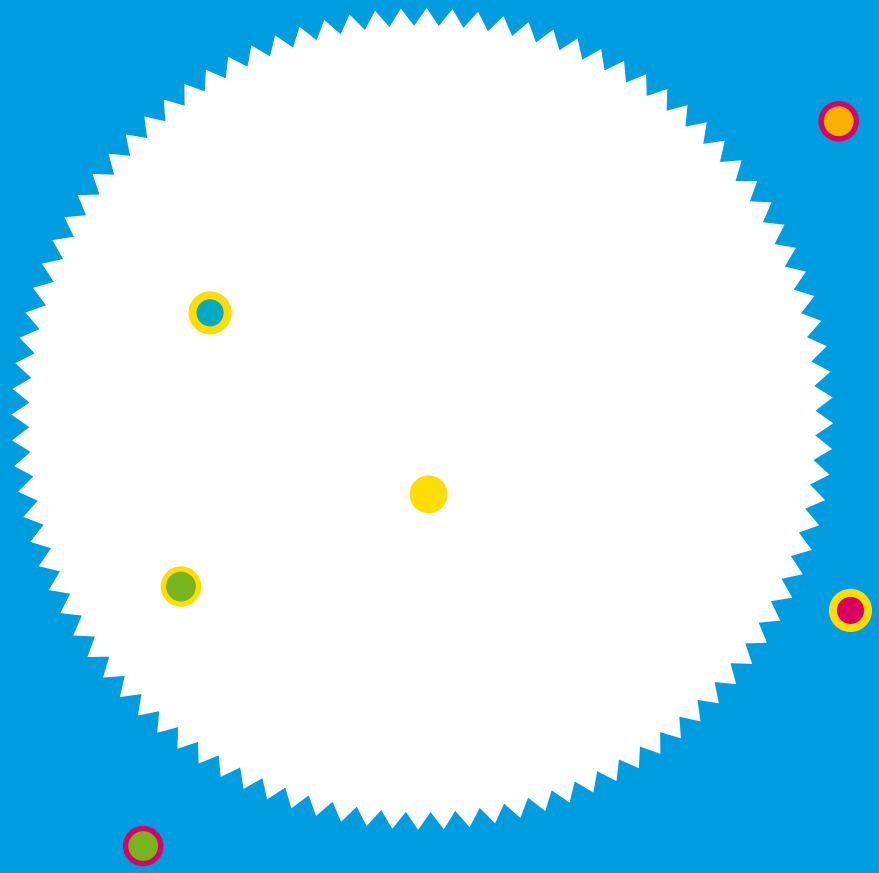
viral rebound: when current treatment fails and viral load starts to rise again.

wild-type virus: HIV that has no drug resistance. This is usually the virus that you are first infected with.

Call us on
0808 800 6013

i-Base Treatment Information Phoneline

Monday to Wednesday
12 noon to 4pm



i-Base can also answer your questions by email or online

questions@i-Base.org.uk
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