

SECTION 4

ANTIRETROVIRAL TREATMENT (ART)

This section provides information about HIV treatment, called antiretroviral treatment (ART).

Who should take ART? What is it, and how does it work? What is the goal of ART? What side effects does it have? How can you tell whether ART is working? What happens if ART stops working?

After reading this section, you will have a basic understanding of:

- » Who should receive ART
- » What ART is and how it works
 - The goal of ART – an undetectable viral load
 - Antiretroviral (ARV) classes
 - ARVs recommended by WHO and in South African Treatment Guidelines
 - Side effects
- » Adherence and drug resistance
 - What adherence is
 - What drug resistance is
- » First-line treatment
 - How to tell if ART is working
 - What can be done if your ART stops working
 - Second-line treatment
 - Third-line treatment





WHO SHOULD BE TREATED FOR HIV?

A combination of medicines, called antiretroviral treatment (ART), is recommended for all infants, children, adolescents and adults who are living with HIV.

ART is recommended because it has been proven to improve health and quality of life among millions of people living with HIV – and it can give them a normal lifespan.

Now that HIV treatment is so effective, and side effects often mild, it is especially important to know whether you are HIV positive. ART works for everyone, no matter their age, gender or how they got HIV, so long as it taken on a daily basis.



People may need support and information to prepare them to start ART since it is currently lifelong. This includes understanding that:

- » You need to feel ready to start, and committed to stay on ART;
- » ART will help you stay healthy by keeping your immune system strong – or allowing it to rebuild;
- » Side effects from newer antiretroviral (ARV) drugs are often mild and can usually be managed;
- » Taking every dose of ART and following food recommendations gives you the best chance of successful treatment.

WHAT IS ART AND HOW DOES IT WORK?

ART is a combination of usually three different ARV medicines. These ARVs stop HIV from being able to enter CD4 cells or stop it from being able to multiply once it is inside of CD4 cells.

The goal of ART is to reduce the amount of HIV in your bloodstream until it is so low that a viral load test cannot find it – called undetectable. An undetectable viral load helps people to stay healthy, and it can also reduce HIV transmission. People who have an undetectable viral load (less than 200 copies/mL) do not transmit HIV to their sex partners.

An undetectable viral load does not mean that someone has been cured from HIV, but it does mean that treatment is working. ART is not a cure, because it does not get rid of all the virus in a person's body. HIV also lives in resting cells, where ARVs cannot reach it. If a person stops taking ART, their viral load will increase.

TYPES OF ARVs

There are different families, or classes of ARVs. They were made to block different steps of HIV the life cycle. Each class of drugs stops HIV from reproducing. Using a combination of drugs works because each one is actively fighting the virus in a different way.

In South Africa, for first-line ART, we usually take our ARVs combined in a single pill – this is called a fixed-dose combination or FDC.

Many individual ARVs are also available as single pills.

Generic versions of HIV drugs work just as well as those from the originator manufacturer. In the public sector in South Africa, most of the ARVs are generic.

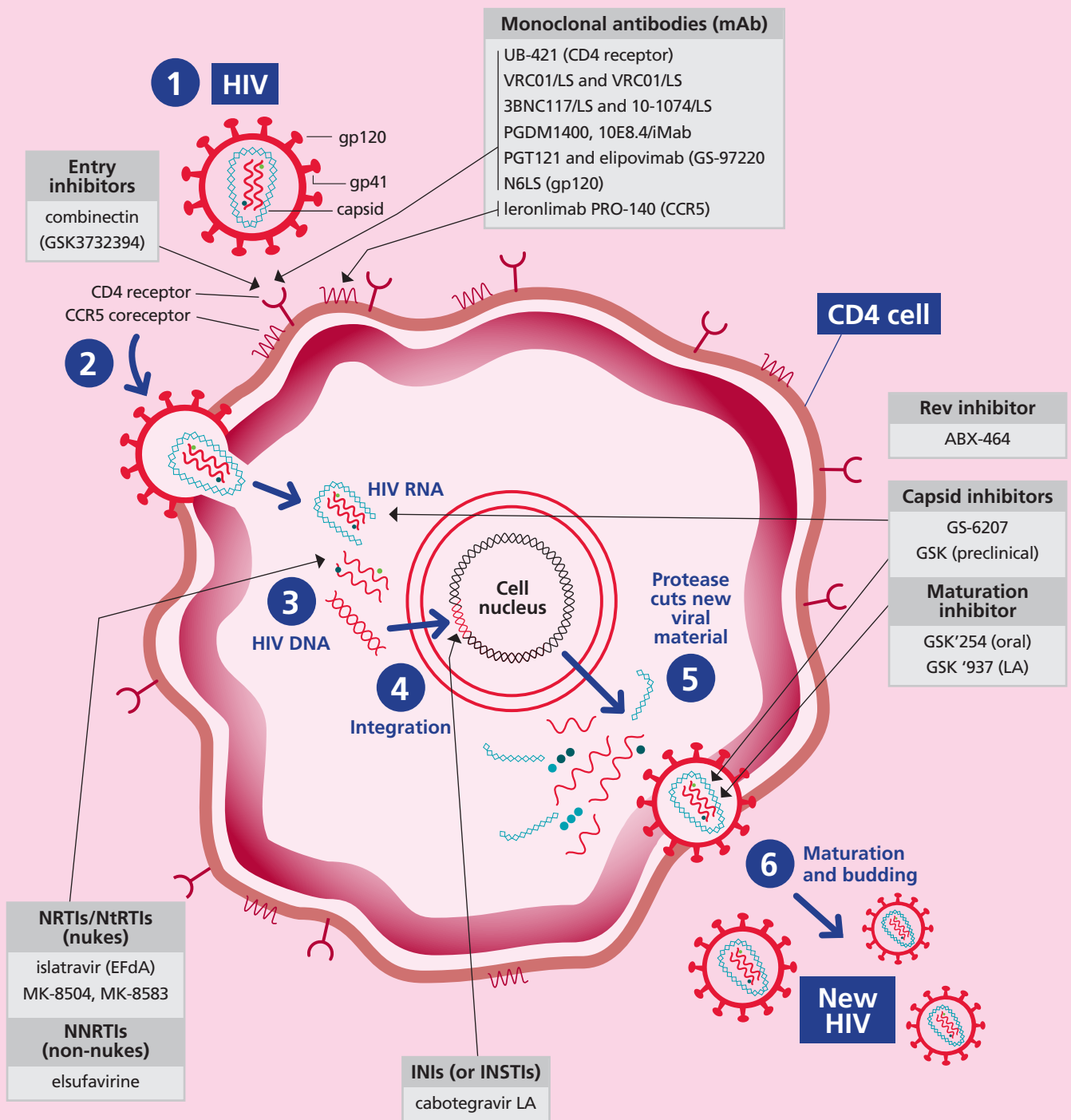
TABLE 1. WHO-RECOMMENDED ARVs IN SOUTH AFRICA'S HIV TREATMENT GUIDELINES, by CLASS

CLASS	NAME
Integrase strand transfer inhibitors (integrase inhibitors or INSTI)	Dolutegravir (DTG) Raltegravir (RAL)
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)	Efavirenz (EFV) Nevirapine (NVP)
Nucleoside/tide Reverse Transcriptase Inhibitors (NRTI)	Abacavir (ABC) Emtricitabine (FTC) Lamivudine (3TC) Tenofovir (TDF) Zidovudine (AZT)
Protease inhibitors (PI)	Atazanavir/ritonavir (ATZ/r) Lopinavir/ritonavir LPV/r)

HIV ENTRY, ATTACHMENT AND FUSION INHIBITORS

These drugs are sometimes available in the private sector (and used very rarely). They are not included in South African or WHO HIV treatment guidelines, because of high prices, need for additional testing and/or because they are given by injection or infusion.

TARGETS IN THE HIV LIFECYCLE



- 1 HIV attaches to a CD4 cell.
- 2 HIV enters a CD4 cell and HIV proteins and enzymes are released into the cell.
- 3 Reverse transcriptase (RT) makes double strand HIV.
- 4 Integrase enables HIV to join the cell DNA.
- 5 Protease cuts and reassembles new HIV.
- 6 Final stages include maturation and budding as each cell produces hundreds of new virions.



SIDE EFFECTS

People often have concerns about ART side effects. They are usually mild, although they differ for each person. The most common side effects are nausea, diarrhoea, dizziness, headache, strange dreams and feeling tired. These side effects tend to lessen over days to weeks after starting ART, and some can be treated with other medicines.

EFV can cause changes in your mood, vivid dreams, disorientation (being unsure where you are), anxiousness and dizziness. Sometimes it can worsen depression or cause nightmares.

DTG has fewer side effects than EFV. It often causes weight gain – especially in women – and although it is less common, DTG can cause insomnia and mood changes.

DTG has also been linked to neural tube defects in babies whose mothers took DTG around the time of conception (called periconception). It is important to note that this happens very rarely. But there are a few extra things for women of child-bearing potential (meaning you plan to have a baby or could get pregnant) to consider. We will look at ART in pregnancy and explain more about the benefits and risks in our section on HIV and pregnancy.

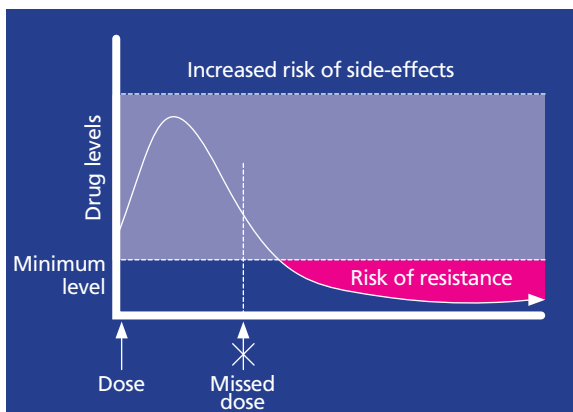
If you are having persistent side effects that make it difficult for you to take your ARVs, discuss them with your nurse or doctor. ARVs can often be changed, and sometimes other illnesses can be causing these symptoms. Serious side effects are rare; if they occur, instead of stopping your ARVs, immediately seek care at a clinic.



ADHERENCE

Adherence means sticking to something – in this case, ART. Taking your ARVs every day as prescribed, including with or without food, gives you the best chance for successful treatment.

This is because a certain level of ART must be in your body every day to be effective. If your drug levels are too low, then the drug will not do anything – and there is a risk of resistance (when it will not work even when taken every day, see below). If drug levels are too high, then side effects are more likely, or they can be worse.



Taking your ARVs around the same time each day keeps the level of each drug high enough to fight HIV. If your ARVs need to be taken with food, make sure to eat – taking them on an empty stomach can be like only taking half a dose. You will not absorb enough of the drug for it to work.

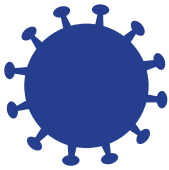
Occasionally (such as once a month) missing or being late with a dose may not make much difference. But if you are missing doses, or taking them late even once a week, consider our adherence tips to avoid developing resistance over time.

ADHERENCE TIPS

It is important to get information and advice to help you adhere to your treatment, such as:

- » The number and size of tablets and how many times a day do you need to take them. For most people though, especially on first-line, modern ART is just one pill once a day.
- » If it/they need to be taken with or without food
 - Taking pills can become part of your daily routine, just like brushing your teeth
 - An alarm can help remind you to take your ARVs
 - Ask your family or friends for help with reminders to take your ARVs
 - Plan ahead: if you are going away, take extra pills with you
- » How to store them
 - Try to keep your pills in the same place
 - Keep an emergency supply with a friend. But remember to keep them in a cool spot and replace them before they get too old.
- » What the side effects are
 - Go to your clinic if you have side effects.

Ask about an adherence club or treatment counsellor at your clinic. If you are in a support group or you know other people who are taking ARVs, ask them for their help.



HIV DRUG RESISTANCE

Drug resistance happens when HIV changes its structure in a way that stops a drug from working. Without ART, HIV makes millions of copies each day. Some of these copies have changes, called mutations. Some mutations are harmless, some of them might weaken HIV, but others can stop ARVs from working.

HIV drug resistance can develop from missing doses, treatment interruptions, drug stockouts and other circumstances. Sometimes people who have taken ARVs in the past – even for a short time – will develop drug resistance. Some people are infected with HIV that is already resistant, even though they have never taken ARVs.

Many people can take ART for years without developing resistance, especially newer ARVs. Since ART prevents HIV from multiplying, it does not have the chance to mutate in people who are undetectable. But if people taking ART have a viral load above 50 copies/mL after six months, resistance can develop. This is why viral load testing is important (see How to tell if ART is working).



FIRST-LINE TREATMENT

This is the first treatment a person with HIV starts taking. First-line treatment is made up of ARVs that are the most effective, have the fewest side effects and are affordable. Some people stay on their first-line treatment for many years.

In South Africa, recommended first-line combinations for adults and adolescents are: tenofovir/lamivudine/dolutegravir (TLD)*, which is preferred, or tenofovir/emtricitabine/efavirenz (TEE).

The recommended first-line combination for children under age 10 is: abacavir/lamivudine/dolutegravir (ABC+3TC+ DTG)

The recommended first-line combination for infants (age 4 weeks to 1 year) is: abacavir/lamivudine/lopinavir/ritonavir (ABC+ 3TC + LPV/r)

The recommended first-line combination for neonates (from birth until 4 weeks) is: zidovudine/lamivudine/nevirapine (AZT + 3TC + NVP).

We will talk more about ARVs and children in our section on HIV and children.

**Women of child-bearing potential, including those who are pregnant, should be provided with pregnancy testing and counseling about the risk of neural tube defects, so that they are enabled to make an informed choice about TEE or TLD. Also, women who do not want to become pregnant need to be offered options for contraception. We will talk more about this in our section on HIV and pregnancy.*

Table 2. South African Guidelines for First-Line ART

	ADULTS (age greater than 19 years) <i>Weight 35 kg or more</i>	ADOLESCENTS (age from 10-19 years)	CHILDREN (age under 10 years)	INFANTS (from 4 weeks to 1 year of age)	NEONATES (from birth to 4 weeks of age)
FEMALE, of child-bearing potential	TLD, with consent or TLE: If planning pregnancy, or up to 6 weeks pregnant TLD: if not planning pregnancy, not currently pregnant or more than 7 weeks pregnant	ABC+3TC+DTG	ABC+3TC+DTG	ABC+3TC+LPV/r	AZT+3TC+NVP
FEMALE, not of child-bearing potential	TLD				
MALE	TLD				

ABC: abacavir; DTG: dolutegravir; LPV/r: lopinavir/ritonavir; NVP: nevirapine; TLD: tenofovir/lamivudine/dolutegravir; TLE: tenofovir/lamivudine/efavirenz; 3TC: lamivudine



HOW TO TELL IF ART IS WORKING

When ART is working, your viral load test result should be undetectable – meaning there is so little HIV in your blood that the test cannot find it.

A viral load test measures the amount of HIV in a blood sample. In South Africa, routine viral load monitoring is recommended six months after starting ART, and for people with a viral load under 50 copies/mL, every 12 months thereafter.

WHAT TO DO IF ART STOPS WORKING

People who have a viral load that is between 50–999 copies/mL should be given extra adherence support and re-tested in three months. People with a viral load that is over 1000 copies/mL need re-testing, adherence support and possibly, switching to a second- or third-line regimen.



SECOND-LINE TREATMENT

Second-line treatment is given when first-line treatment is no longer working. Sometimes, people switch one or more ARVs if their side effects are too bad. The treatment you are given will depend on which ARVs you have already received.

TABLE 3. South African Guidelines for Second-Line ART in Adults

FIRST-LINE	SECOND-LINE
TDF/XTC/EFV or NVP	No coinfection with hepatitis B virus: AZT/XTC/DTG or AZT/XTC/LPV/r Coinfection with hepatitis B virus: add TDF
TDF/XTC*/DTG	No coinfection with hepatitis B virus: AZT/XTC/LPV/r Coinfection with hepatitis B virus: add TDF

AZT: zidovudine; DTG: dolutegravir; EFV: efavirenz; LPV/r: lopinavir/ritonavir; NVP: nevirapine; TDF: tenofovir; XTC: lamivudine (3TC) or emtricitabine

TABLE 4. South African Guidelines for Second-Line ART in Adolescents and Children

FIRST-LINE	RESISTANCE TESTING	SECOND-LINE
ABC/AZT/TDF + 3TC/FTC + EFV or NVP	Not needed	Weight under 20 kg: ABC/AZT/3TC/LPV/r
		Weight over 20 kg : 2 NRTI + DTG If NRTI are not working, consult with expert to select 2 NRTI + LPV/r or ATZ/r
ABC/AZT/TDF + 3TC/FTC + LPV/r or ATZ/r	Required	Weight under 20 kg, no resistance to protease inhibitors: continue the same ARVs, provide adherence support
		Weight over 20 kg, no resistance to protease inhibitors: 2 NRTIs + DTG If NRTI are not working, provide adherence support, consult with expert to select 2 NRTI = LPV/r or ATZ/r
		Weight under or 20 kg, resistant to protease inhibitor: consult third-line committee
ABC/AZT/TDF + 3TC/FTC + DTG	Required	No resistance to integrase inhibitors: 2 NRTI + DTG If NRTI are not working consult third-line committee.
		Resistance to integrase inhibitors: consult third-line committee

ABC: abacavir; ATZ/r: atazanavir/ritonavir; AZT: zidovudine; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir/ritonavir; NVP: nevirapine; TDF: tenofovir; 3TC: lamivudine.



THIRD-LINE TREATMENT

In 2013, South Africa put together a national committee in the public sector to assess eligibility and make individualised recommendations for third-line treatment, based on a person's HIV treatment history and resistance testing. Certain ARVs that have proven to be effective in people who have been on many ARVs, are specifically recommended for third-line: darunavir/ritonavir (DRV/r; a boosted protease inhibitor), etravirine (ETV; a non-nucleoside reverse transcriptase inhibitor) and raltegravir (RAL; an integrase inhibitor).

WHO TREATMENT RECOMMENDATIONS

Table 5: World Health Organization preferred and alternative first-line ART regimens, as on 22 July 2019.

Population	Preferred first-line regimen	Alternative first-line regimen	Special circumstances
Adults and adolescents	TDF + 3TC (or FTC) + DTG	TDF + 3TC (or FTC) + EFV 400 mg	TDF + 3TC (or FTC) + EFV 600 mg AZT + 3TC + EFV 600 mg TDF + 3TC (or FTC) + PI/r TDF + 3TC (or FTC) + RAL TAF + 3TC (or FTC) + DTG ABC + 3TC + DTG
Children	ABC + 3TC + DTG	ABC + 3TC + LPV/r TDF + 3TC + RAL TAF + 3TC (or FTC) + DTG	ABC + 3TC + EFV (or NVP) AZT + 3TC + EFV (or NVP) AZT + 3TC + LPV/r (or RAL)
Neonates	AZT + 3TC + RAL	ABC + 3TC + NVP	AZT + 3TC + LPV/r

Table 6: World Health Organization preferred and alternative second-line ART regimens, as on 22 July 2019.

Population	Failing first-line regimen	Preferred second-line regimen	Alternative second-line regimen
Adults and adolescents	TDF + 3TC (or FTC) + DTG	TDF + 3TC + ATV/r (or LPV/r)	ABC + 3TC + DRV/r
	TDF + 3TC (or FTC) + EFV (or NVP)	AZT + 3TC + DTG	AZT + 3TC + ATV/r (or LPV/r or DRV/r)
	AZT + 3TC (or FTC) + EFV (or NVP)	TDF + 3TC (or FTC) + DTG	TDF + 3TC (or FTC) + ATV/r (or LPV/r or DRV/r)
Children and infants	ABC + 3TC + DTG	ABC (or AZT) + 3TC + LPV/r (or ATV/r)	ABC + 3TC + DRV/r
	ABC (or AZT) + 3TC + LPV/r	ABC (or AZT) + 3TC + DTG	ABC (or AZT) + 3TC + RAL
	ABC (or AZT) + 3TC + EFV	ABC (or AZT) + 3TC + DTG	ABC (or AZT) + 3TC + LPV/r (or ATV/r)
	ABC + 3TC + NVP	ABC + 3TC + DTG	ABC (or AZT) + 3TC + LPV/r (or ATV/r or DRV/r)



QUESTIONS

1. What is antiretroviral treatment (ART) ?
2. Who should take ART?
3. How do antiretrovirals (ARVs) work?
4. What is the goal of ART?
5. What is first-line ART?
6. What is DTG?
7. What is adherence? Why does it matter?
8. How can you tell if your ART is working?
9. What can be done if your ART stops working?

ANSWERS

1. ART is a combination of medicines used to treat HIV.
2. ART is recommended for all infants, children, adolescents and adults living with HIV. ART has been proven to improve the health and quality of life among millions of people living with HIV – and it can give them a normal lifespan.
3. ART stops HIV from being able to enter CD4 cells or stops it from being able to multiply once it is inside of CD4 cells.
4. The goal of ART is to reduce the amount of HIV in your bloodstream until it is so low that a viral load test cannot find it – called undetectable. An undetectable viral load helps people to stay healthy, and it can also reduce HIV transmission, since people with an undetectable viral load (less than 200 copies/mL) do not transmit HIV to sex partners.
5. First-line ART is the first treatment a person with HIV starts taking. First-line treatment is made up of ARVs that are the most effective, have the fewest side effects and are affordable. Some people stay on their first-line treatment for many years.
6. Dolutegravir (DTG) is part of first-line ART. It has fewer side effects than EFV.
7. Adherence means sticking to something – in this case, ART. Taking your ARVs every day as prescribed, including with or without food, gives you the best chance for successful treatment.
8. When ART is working, your viral load test result should be undetectable – meaning there is so little HIV in your blood that the test cannot find it.
9. People with a viral load that is over 1000 copies/mL need re-testing, adherence support and possibly, switching to a second- or third-line regimen.

FURTHER READING

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EXERCISES

[to come]

