

#HIV2022istanbul

Future of HIV drug research

4-6 November 2022



Simon Collins (i-Base.info)



#CivilSocietyHasTheAnswer

Overview

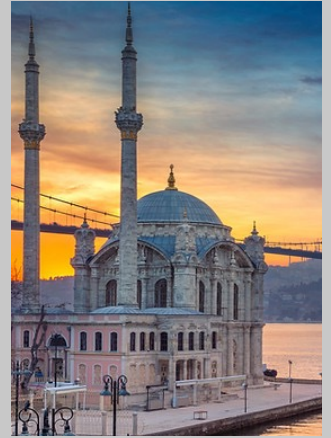
Why activism?

History of HIV drug development.

Current modern ART.

HIV pipeline: next generation ART.

Overlap of prevention, treatment and cure.



Why activism?

Changes can make life better:
for you, for your friends,
for people living with HIV.

*You see a better way to do things, then
decide to help make it happen, more quickly.*

Community, scientists, doctors, funders...



HIV examples...



Denver Principles.

Doctors & nurses who ignored prejudice.

Scientists, researchers, manufacturers.

Fundraising. Better care in hospitals.

Direct action: ACT-UP and AZT price.

Global access, PrEP research, U=U.

Denver principles (1983)

- Put people with HIV at the centre of care.
- Self empowerment, rights, dignity, respect.
- Involvement in all decisions
- Language: “**People** living with HIV/AIDS”.



<https://i-base.info/qa/factsheets/the-denver-principles-1983>

People first language

- Words are important.
- Many health conditions - not all - want to emphasise the person first:
- “Person living with HIV...”
- NOTL victim, patient, HIV-infected or PLWH.
- An HIV negative person is not “healthy”

www.en.wikipedia.org/wiki/People-first_language

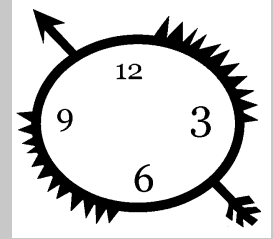
www.peoplefirstcharter.org

Being an active patient



1. You have the best interest in your health.
2. Learning about ART makes talking to your doctors easier.
3. Taking an active role in your health means you share responsibility. Tracking research lets you plan ahead.

ART timeline



1981-1986: No ARVs.

1987-1995: AZT, ddI, ddC and d4T

1996-2000: early HAART: viral load, many pills, many side effects. High cost.

2000-2008: better drugs, 2nd-generation PIs and NNRTIs. Atripla (FDC), raltegravir (INSTI).

2009-2022: 2nd-gen INSTIs. 10 FDCs. Injectable ART.

2015: START study - treat at any CD4 count

35 ARVs in US/Europe (+ FDCs)

- AZT 1987
- ddI 1991
- ddC 1992
- d4T 1994
- 3TC 1995
- saquinavir 1995
- indinavir 1996
- ritonavir 1996
- nevirapine 1996
- delavirdine 1997
- nelfinavir 1997
- efavirenz 1998
- abacavir 1998
- amprenavir 1999
- lopinavir 2000
- tenofovir 2001
- T-20 2003
- atazanavir 2004
- fosamprenavir 2004
- FTC 2004
- tipranavir 2005
- Kaletra (meltrex) 2006
- Atripla 2006
- darunavir 2006
- maraviroc 2007
- raltegravir 2007
- etravirine 2009
- rilpivirine 2011
- dolutegravir 2013
- elvitegravir 2014
- F/TAF 2016
- bictegravir 2017
- ibalizumab 2018
- fostemsavir 2020
- Cabenuva 2021
- lenacapavir 2022

ART in 2022: 10 single tablets + 1 injectable ART



Atripla



Biktarvy



Delstrigo



Dovato



Eviplera



Juluca



Odefsey



Stribild



Symtuza



Triumeq



CAB-LA +
RPV-LA
injections

Limited access to some based on pricing.

Ref: HIV pipeline report 2021; i-base.info/htb/41142

Timeline for ART access

1998: “HIV drugs are not for Africa”

2003: *Triomune (Cipla) generic single pill FDC.*
\$1 a day. WHO 3x5 campaign.

2006: Atripla single pill FDC: efavirenz/TDF/FTC.
\$10,000 a year

2017: *Generic integrase inhibitor single pill FDC.*
TLD=tenofovir/lamivudine/dolutegravir: \$75 a year.

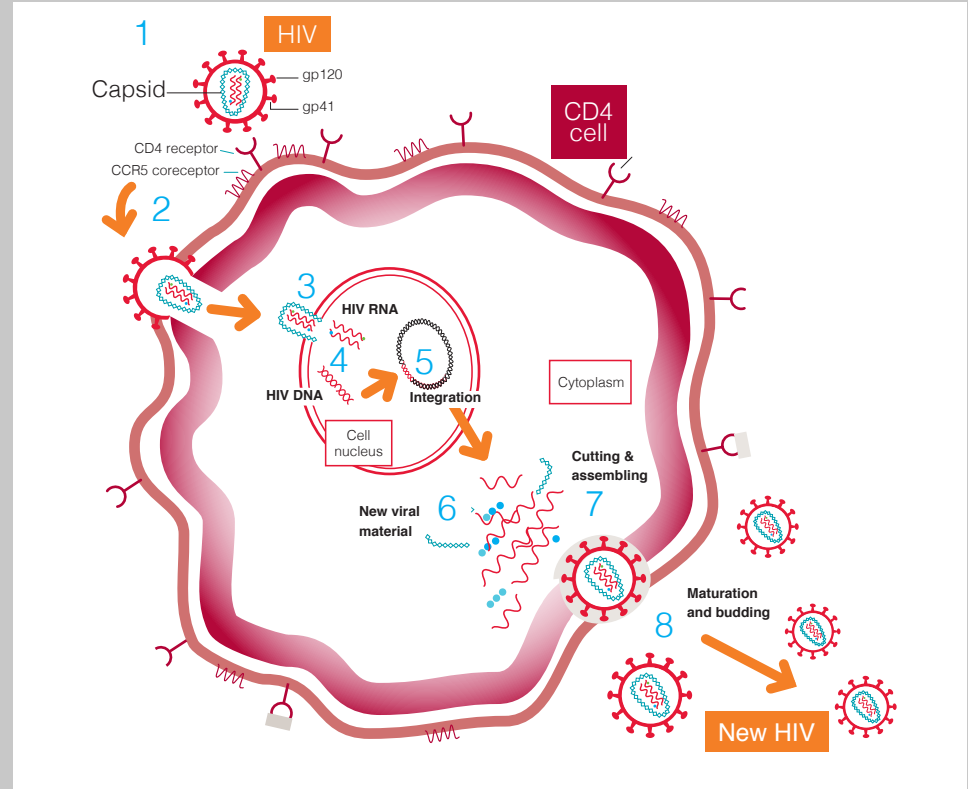
2022: 28 million people on ART



HIV lifecycle

Stages where
drugs can work

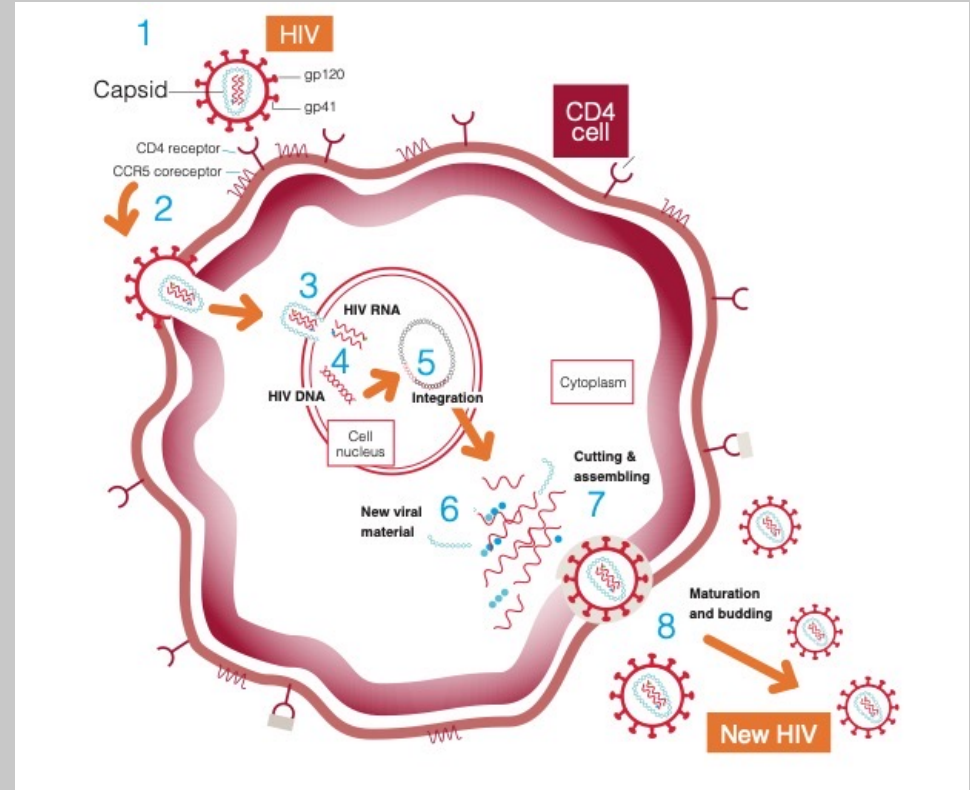
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i-base.info/htb/41142



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HIV lifecycle in detail

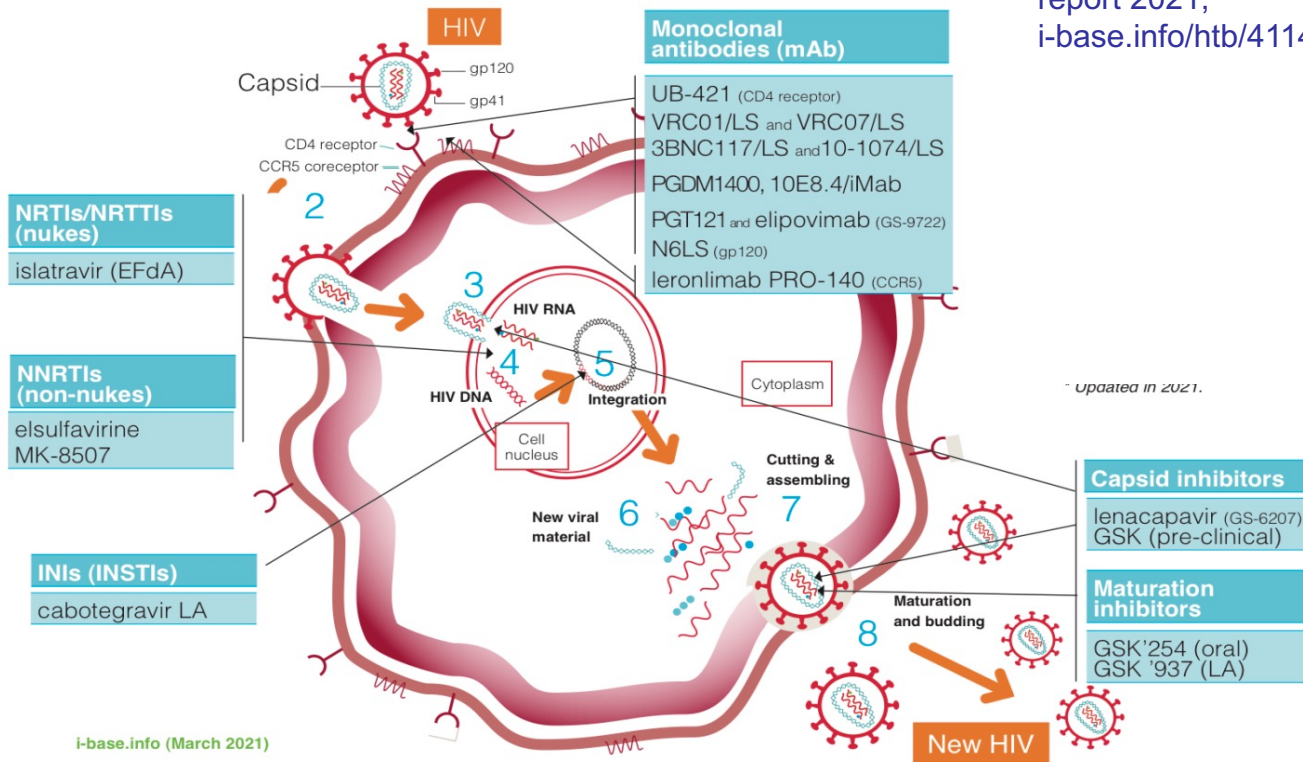
1. HIV attaches to a CD4 cell.
2. HIV enters a CD4 cell.
3. The capsid enters the cell nucleus where HIV proteins and enzymes are released.
4. Reverse transcriptase (RT) makes double strand HIV.
5. Integrase enables HIV DNA to join the cell DNA.
6. New viral material is made.
7. Protease cuts and makes new HIV.
8. Each cell makes hundreds of new virions.



Ref: HIV pipeline report 2021; i-base.info/htb/41142

HIV pipeline 2021: targets in the HIV lifecycle

Ref: HIV pipeline
report 2021;
i-base.info/htb/41142



Treatment pipeline

- Lenacpavir
- islatravir
- GSK254 - fipravirimat - maturation inhibitor
- bNAbs – many different types

HIV prevention

- Oral TDF/FTC:
Daily dosing and 2:1:1 on demand dosing.
- Long-acting cabotegravir injections - 2 monthly

WHO include PrEP as an essential option to protect against HIV.

Lenacpavir

- Capsid inhibitor.
- New class.
- Subcutaneous injection every 6 months.
- Needs to be used with other active drugs.
- Approved in 2022 for people with multidrug resistance.
- Weekly oral formulation (with islatravir).

Islatravir

- NRTTI (similar to nukes).
- Highly potent – daily dose: 0.25 mg.
- Originally for treatment and long-acting prevention (monthly oral and yearly implant).
- Studies paused last year for reducing CD4 count, now restarted with lower dose.
- Weekly oral formulation (with lenacapavir).
- Prevention: now with MK-8527.

GSK254 - fipravirimat

- Maturation inhibitor (last stage).
- Oral drug. New class.
- Originally for treatment and long-acting prevention (monthly oral and yearly implant).
- Studies paused last year for reducing CD4 count, now restarted with lower dose.
- Weekly oral formulation (with lenacapavir).

Pipeline formulations

- weekly pills.
- long-acting injections.
- infusions (3-6 monthly).
- Monthly pills (PrEP) ?
- Implants, rings, patches, gels, douches (PrEP) ?

bNAbs

Broadly neutralizing monoclonal antibodies

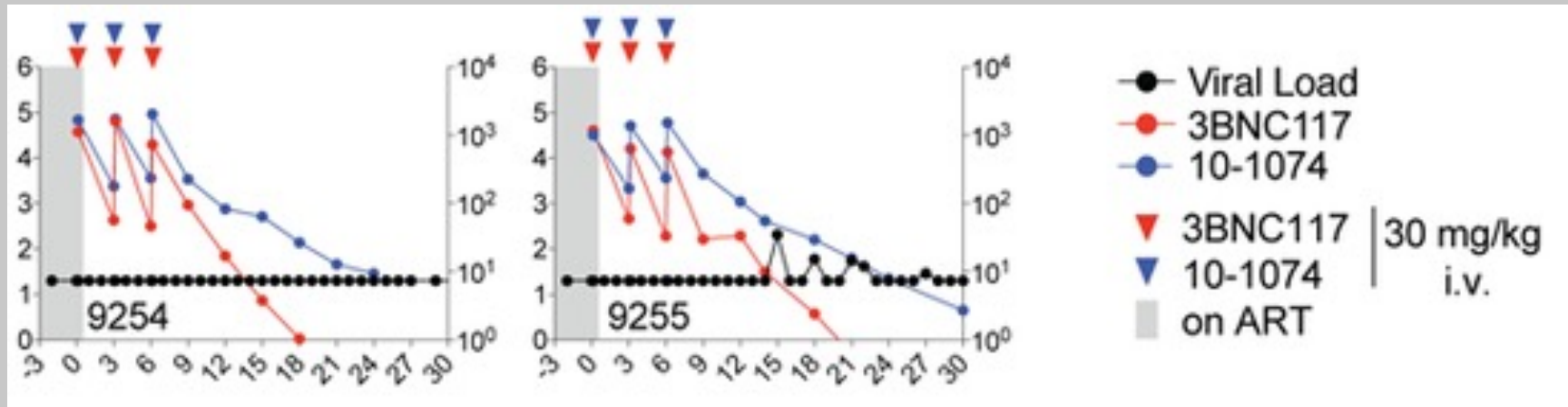
- Isolated from people with strong immune responses to HIV. Adapted in long-acting formulations
- Active against HIV and boost immune system.
- Used as treatment and for prevention

Immune-based drugs

- Long-acting bNAbs: 3BNC117 & 10-1074 (Gilead),
N6LS (ViiV)
- Antiviral effect and possible vaccine effect.
- Need baseline sensitivity test and use in combinations.
- Used for treatment and prevention.
- Infusion every 3 – 6 months.
- Might allow breaks from ART – RIO study and others.

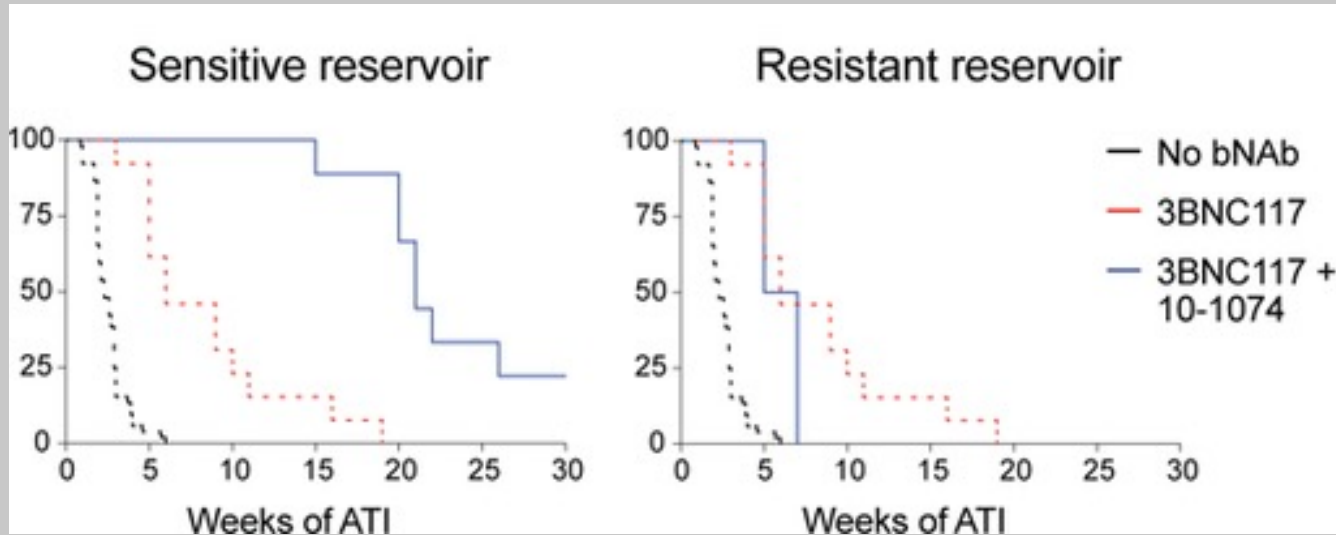
Dual bNAbs

Two participants off-ART >1 year



Mendoza P et al. Nature, 2018
www.nature.com/articles/s41586-018-0531-2

bNAb sensitivity



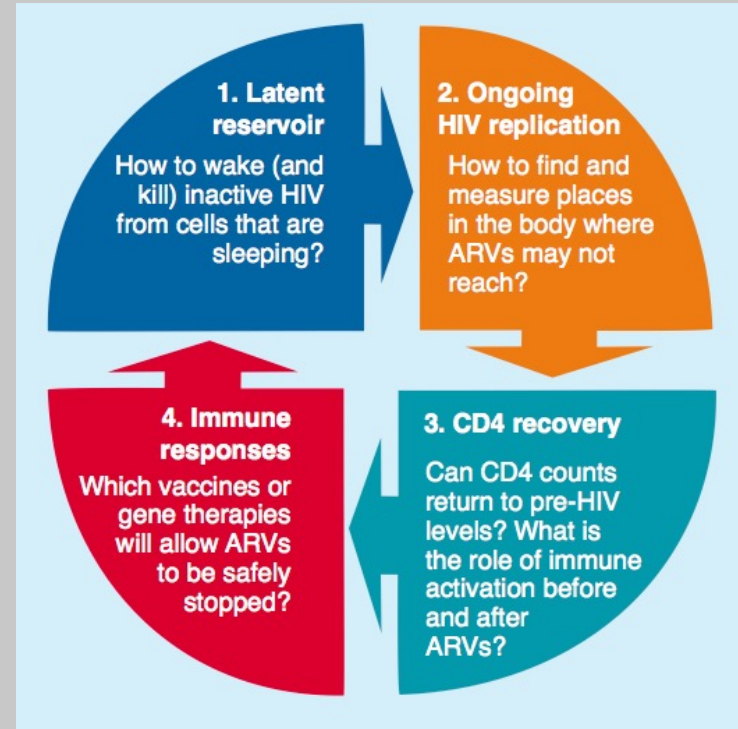
Mendoza P et al. Nature, 2018
www.nature.com/articles/s41586-018-0531-2

Future cure...?

International focus on cure-related research.

- (i) Eradication (cure) or
- (ii) Remission (viral load stays undetectable without ART).

IAS: Roadmap for an HIV cure (Nature, 2021)



Teşekkür ederim...

Questions:

i-base.info/qa

i-base.info/qa/ask-a-question



i-base
HIV treatment
information
service

Calls are free from
land lines and most
mobile networks.
All calls are
confidential.

ASK A QUESTION
by phone, email or online
0808 800 6013
questions@i-base.org.uk
www.i-base.info

Information to be used in discussion with your doctor. Registered charity no: 1081905.

Practical ART

ART = antiretroviral therapy

- Drug classes and HIV lifecycle
- Combinations and choice
- Adherence and drug resistance
- Side effects
- Trans health, children
- ART access and drug pricing.

Ref: Introduction to ART; www.i-base.info/guides/starting



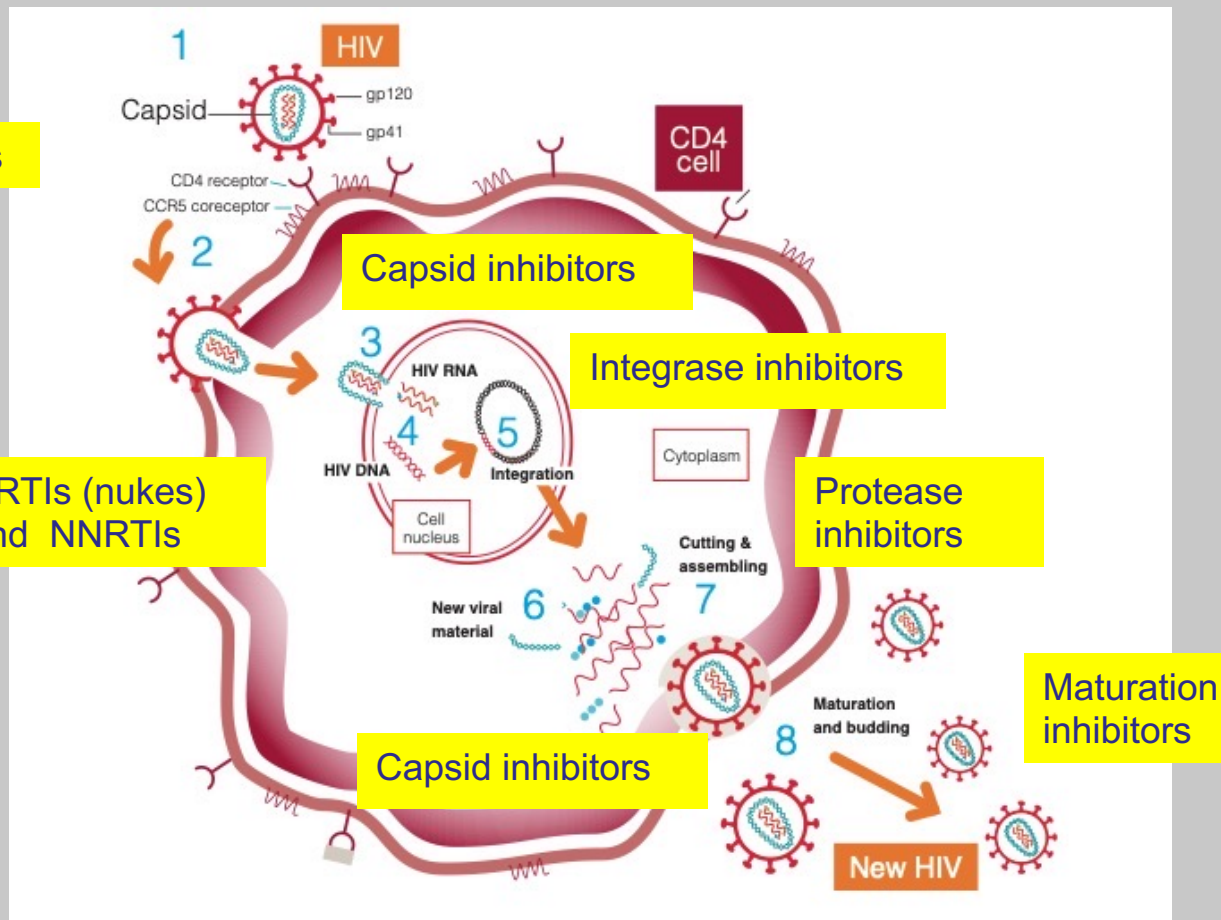
Additional slides

Drug targets

Entry inhibitors

1. Entry inhibitors.
3. Capsid inhibitors.
4. NRTIs (nukes) and NNRTIs.
5. Integrase inhibitors
6. Protease inhibitors
7. Capsid inhibitors
8. Maturation inhibitors

Ref: HIV pipeline report 2021; i-base.info/htb/41142

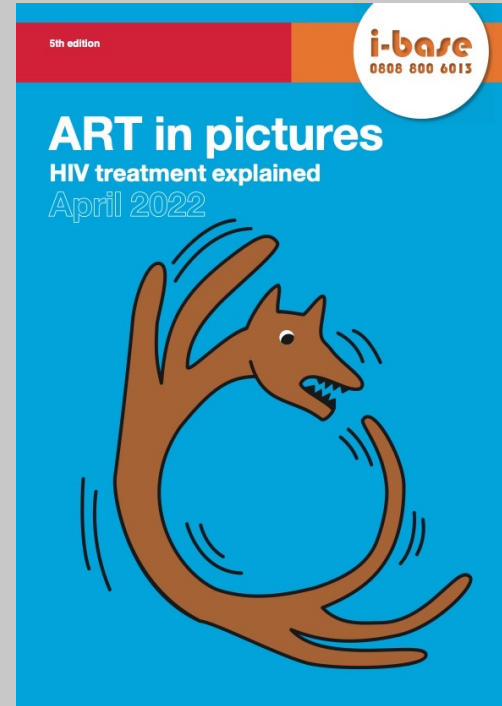


Principles of ART

ART = antiretroviral therapy

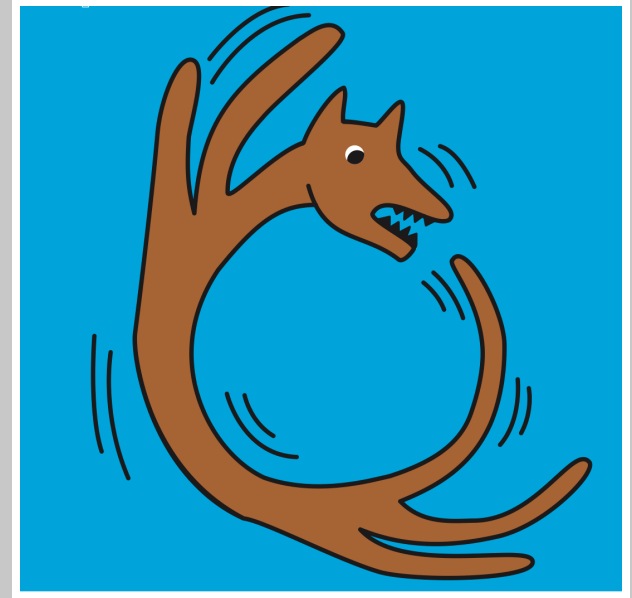
- Types of infections
- Why HIV is tricky
- HIV on and off ART
- CD4 and viral load

Ref: ART in pictures; i-base.info/guides/art-in-pictures



Immune system off-ART

- When not on ART – the immune system is always over-active.
- Like a dog chasing it's own tail!
- !n 2006, the SMART study showed this immune activity increased risk of serious heart/liver/cancer problems.
- SMART showed ART was safer than being off-ART.



Ref: ART in pictures; i-base.info/guides/art-in-pictures. SMART trial: <https://i-base.info/htb/5729>

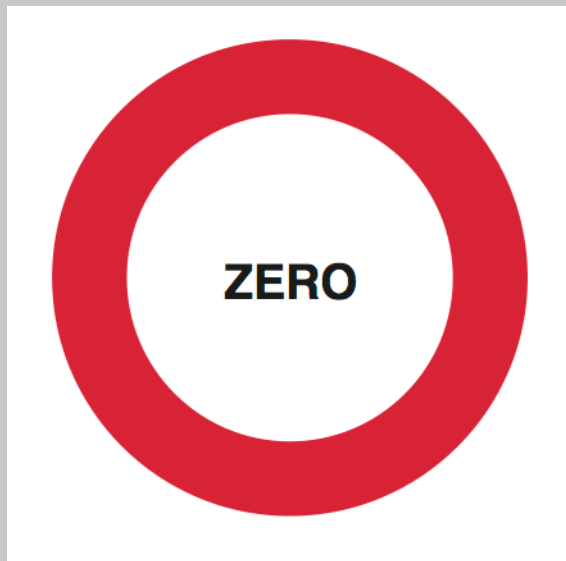
An undetectable viral load on ART

1. Protects the person living with HIV.
2. Protects their sexual partners.



- Viral load <50 copies/mL for 3–6 months.
- Good adherence - not missing doses.

PARTNER studies



PARTNER 1: zero transmissions after gay and straight couples had sex more than 56,000 times ^[1]

PARTNER 2: zero transmissions after gay couples had sex more than 77,000 times ^[2]

1. Rodgers A et al. CROI 2014 and JAMA 2016; 2. Rodgers A et al, IAS 2018 and The Lancet, 2019.

RIO study

- 70 participants diagnosed in early infection and started early ART.
- Undetectable viral load for >6 months.
- Randomise to bNAb or placebo for 24 weeks.
- Stop ART until viral load is either >1000 for six weeks or confirmed >100,000.
- Potential to stay undetectable off-ART for more than 6 months.

Formulations

Long acting injections or infusions.

Slow release microneedle patches.

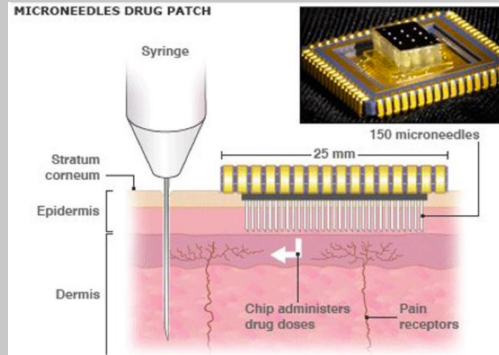
Implants etc.

Already used for *contraception (choice)*, bone health (*convenient*) and schizophrenia (*adherence*),

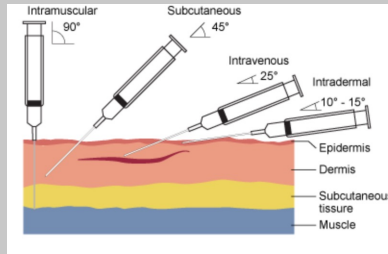


Alternatives to oral pills

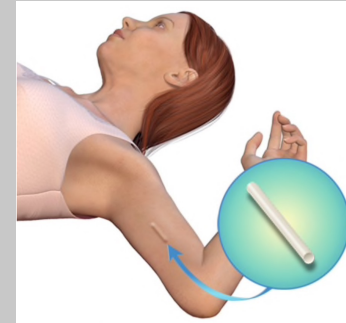
Microneedle drug patch



Long-acting depot injections



Implants

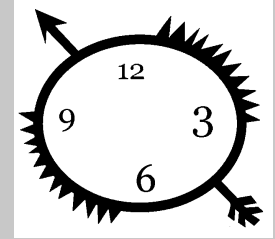


Vaginal rings



Thanks to Kim Scarsi

Workshop working



Please ask questions

- What you already know.
- Which things are difficult.
- What else you want to know.

Please write notes:

- Easier to learn and remember.

Treatment pipeline

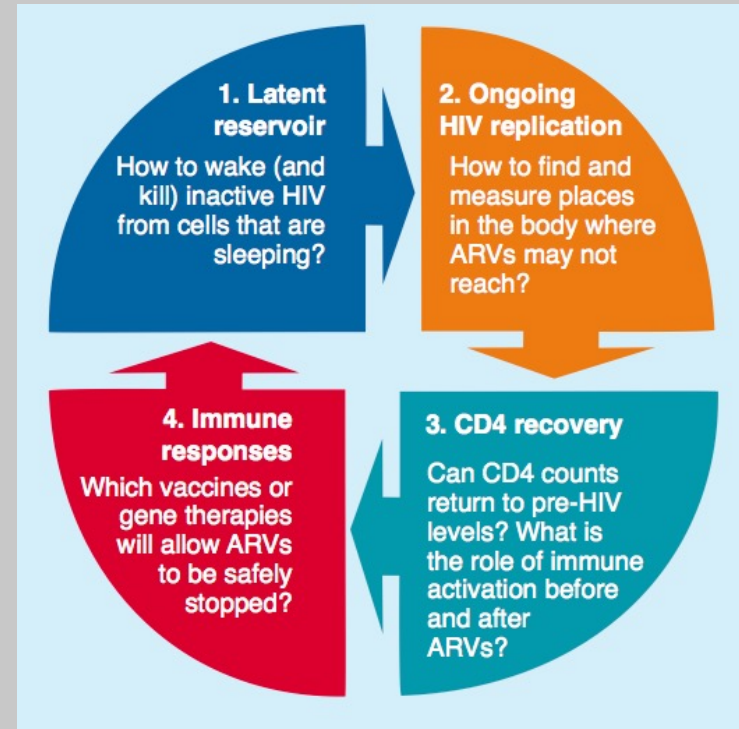
- New drugs: lenacpavir, islatravir, maturation inhibitor, bNAbs.
- New formulations: weekly or monthly oral pills, long-acting injections, implants and infusions (3-6 monthly).
- Immune-based treatments – bNAbs might allow breaks from ART.



Future cure...?

New international focus on cure-related research.

(i) Eradication (cure) or
(ii) Remission (where viral load stays undetectable without need for ART).



Questions?

i-base.info/qa

i-base.info/qa/ask-a-question

A vertical poster with a light blue background. At the top left is the 'i-base' logo in white, with 'HIV treatment information service' in smaller blue text below it. To the right of the logo, in white text, is the statement: 'Calls are free from land lines and most mobile networks. All calls are confidential.' In the center is a large white pill shape with an orange band around its middle. Below the pill, the text 'ASK A QUESTION' is written in large white capital letters, followed by 'by phone, email or online' in smaller white text. Below that is the phone number '0808 800 6013' in large white digits. Underneath the phone number are the email address 'questions@i-base.org.uk' and the website 'www.i-base.info' in white text. The bottom of the poster has a dark blue horizontal band containing a small yellow circle icon and the text 'Information to be used in discussion with your doctor. Registered charity no: 1081905.' Several small, colorful circles (yellow, green, pink) are scattered around the central pill graphic.

i-base
HIV treatment
information
service

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Additional slides

Combinations and choice

Limited access to some based on pricing.

Ref: Introduction to ART; www.i-base.info/guide/s/starting

Antiretroviral drugs 2022/23

www.i-base.info

Drug names	Recommended adult dose *	Total daily pills
Fixed dose combinations		
Approximate to actual size.		
Atripla (efavirenz + emtricitabine + tenofovir DF)	One tablet, once-daily. Take at night and not with a high fat meal. See info on separate drugs.	1
Biktarvy (bictegravir + TAF + emtricitabine)	One tablet, once-daily. Take with or without food. See info on separate drugs.	1
Eviplera (rilpivirine + emtricitabine + tenofovir DF)	One tablet, once-daily, with food (400 kcal). See separate drug info.	1
Odefsey (rilpivirine + emtricitabine + TAF)	One tablet, once-daily, take with food. See info on separate drugs.	1
Triumeq (dolutegravir + abacavir + lamivudine)	One tablet, once-daily. Take with or without food. See info on separate drugs.	1
Genvoya (elvitegravir + cobicistat + emtricitabine + TAF)	One tablet, once-daily. Take with food. See info on separate drugs.	1
Stribild (elvitegravir + cobicistat + emtricitabine + tenofovir DF)	One tablet, once-daily, take with food. See info on separate drugs.	1
Symtuza (darunavir + cobicistat + emtricitabine + TAF)	One tablet, once-daily, take with food. See info on separate drugs.	1
Delstrigo (dorzavirine + lamivudine + tenofovir DF)	One tablet, once-daily, with or without food. See info on each drug.	1
Dovato (dolutegravir + lamivudine)	One tablet, once-daily, with or without food. See info on each drug.	1
Juluca (dolutegravir + rilpivirine)	One tablet, once-daily, take with food. See info on separate drugs.	1

Dual nukes: nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs)

tenofovir DF 300 mg + emtricitabine 200 mg (Truvada [pictured] or generic) **	One tablet, once-daily.	1
TAF (10 mg white or 25 mg blue) + emtricitabine (200 mg), Descovy	One tablet, once-daily.	1
abacavir 600 mg + lamivudine 300 mg (Kivexa or generic) **	One tablet, once-daily.	1

Injectable ART (cabotegravir/rilpivirine long-acting injections (CAB/RPV-LA) and single nukes

See back page for info on injectable ART. Also for single nukes (which are rarely used).

* Different doses or formulations might be used - always check doses with your pharmacist.

** Generic versions might be a different colour and shape. § EU approval pending.

NNRTIs: non-nucleoside reverse transcriptase inhibitors (non-nukes)

efavirenz 600 mg or 200 mg (Sustiva, [pictured] or generic) **	1 x 600 tablet (or 3 x 200 caps) once-daily; at night, not with high fat meal.	1 tablet (or 3 capsules)
nevirapine PR 400 mg (Viramune [pictured] or generic) **	1 x 400 mg once a day. Take with or without food.	1 x 400 mg
etravirine (100 mg or 200 mg) (Intelecto)	2 x 100 mg OR 1 x 200 mg, twice daily, take with food. Dispersible in water.	2 or 4
rilpivirine (Edurant)	1 x 25 mg tablet, once-daily, take with main meal (500 kcal).	1
dorzavirine (Pileitro)	1 x 100 mg tablet, once-daily, take with or without food.	1

INIs or INSTIs: integrase inhibitors

raltegravir 400 mg (pink) & 600 mg (yellow) (Isentress)	1 x 400 mg, twice-daily OR 2 x 600 mg tablet, once-daily. Take with or without food.	2
dolutegravir (Tivicay) *	1 x 50 mg tablet, once-daily (or 1 x 50 mg twice-daily). With food if twice-daily but with or without otherwise.	1 or 2
elvitegravir and bictegravir are only in combination pills - see Stribild, Genvoya and Biktarvy.		

Injectable long-acting cabotegravir-LA (Vocabria) and rilpivirine - LA (Rekamby)

Cabotegravir + rilpivirine-LA (Vocabria + Rekamby)	not to scale	Given as two injections into muscle (into the buttocks) every two months.	none
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b/Pi: boosted protease inhibitors

atazanavir * (Reyataz)	1 x 300 mg cap + booster, once-daily. Take with food. 150 mg and 200 mg capsules also available.	1 (+ 1 booster)
darunavir 600 mg (orange) & 800 mg (red), Prezista *	1 x 800 mg + booster once-daily (OR 1 x 600 mg + 100 mg booster twice-daily with resistance). Take with food.	1 or 2 (+ 1 or 2 boosters)
atazanavir/cobicistat (Evotaz)	1 tablet, once-daily. Take with food.	1
darunavir/cobicistat (Rezolsta)	1 tablet, once-daily. Take with food.	1

PK (pharmacokinetic) boosters

cobicistat (c) (Tybost)	150 mg tablet, once daily. Used to boost atazanavir, darunavir and elvitegravir.	depends on boosted drug
ritonavir (r) * (Norvir)	100 mg tablets used at different doses to boost other PIs.	depends on PI

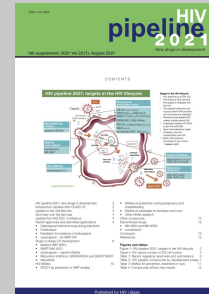
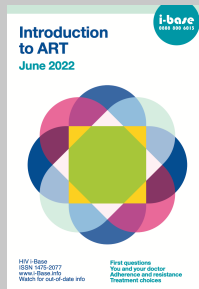
More info and links

- Introduction to ART
- ART in pictures
- HIV and pregnancy
- Changing treatment
- Side effect and quality of life
- Pipeline report 2021

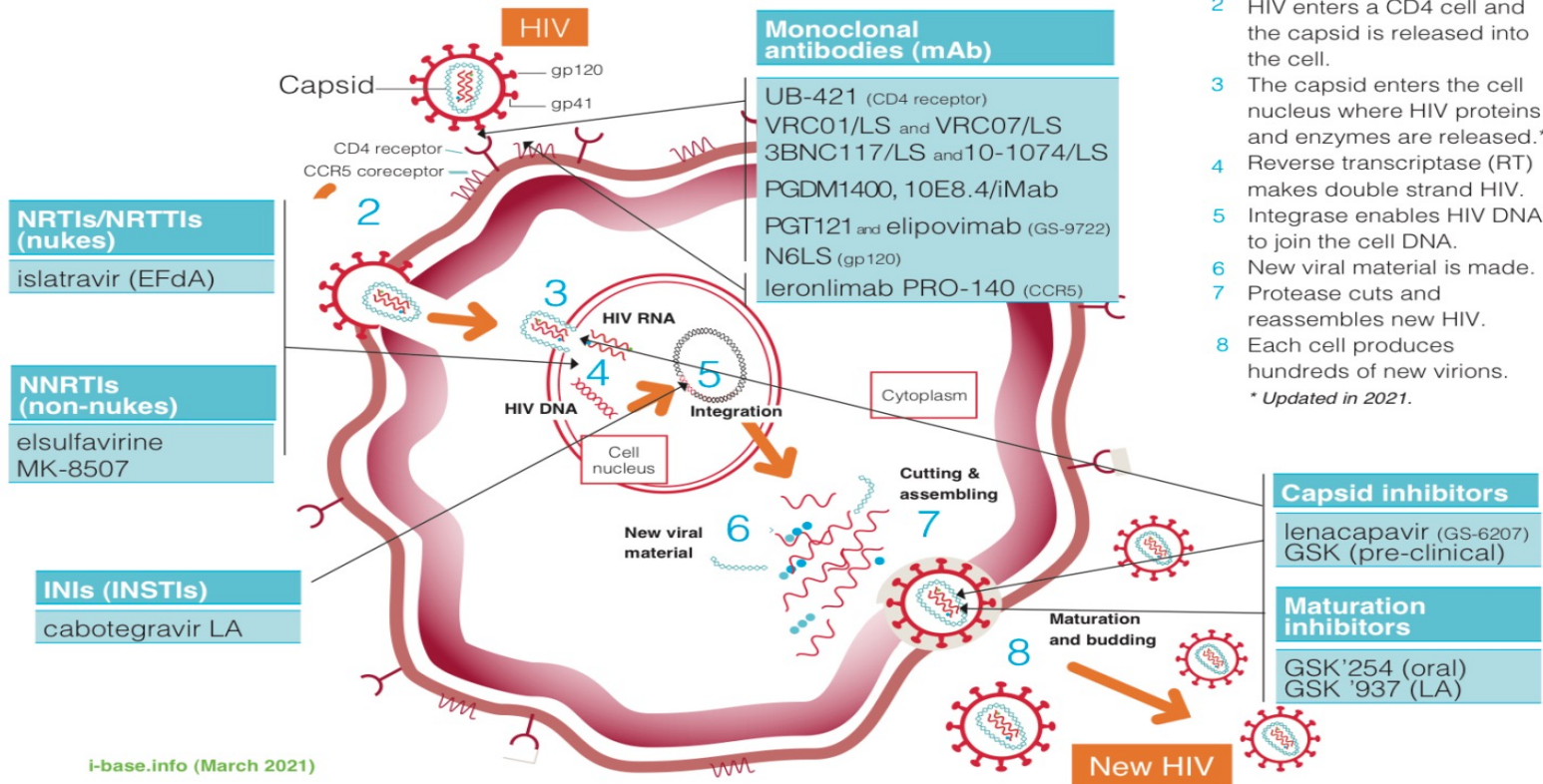
www.i-Base.info

EACS – EU guidelines eacsociety.org

BHIVA – UK guidelines www.bhiva.org



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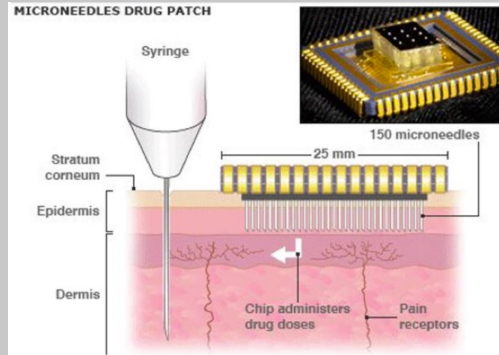
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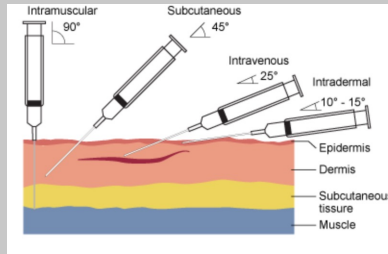


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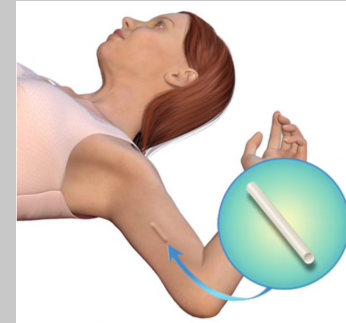
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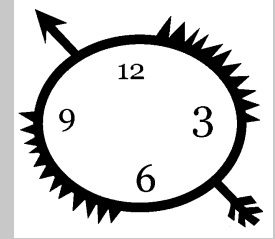


Vaginal rings



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Workshop working



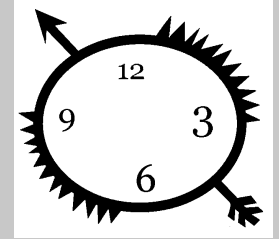
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Please write notes:

- Easier to learn and remember.

HIV science for the community



Why science: goals and introductions

Part 1:

Principles of ART

Wny science?

Evidence vs opinion



Wny science?

Evidence vs opinion

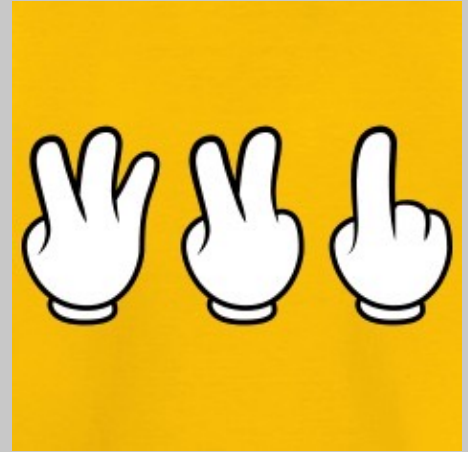
- Essential
- Question everything
- Design **repeatable** studies...
- Recognise reliable sources - for how science is reported.
- Reference the evidence for what you say.



Why science?

The scientific approach to understanding the world usually involves three stages.

1. Observe something.
2. Question why - a hypothesis.
3. Run an experiment to test this idea.



Why science?

The scientific approach to understanding the world usually involves three stages.

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 2. Question why - a hypothesis.
 3. Run an experiment to test this idea.
- ... and then explain/report the story...

