HIV pipeline for PrEP

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HIV Prevention England Conference
18 February 2020

Disclosure

No personal financial conflicts of interest.

Community representative on RIO study.

i-Base receives financial support for some projects from several drug companies including Gilead, Janssen, Merck and ViiV.

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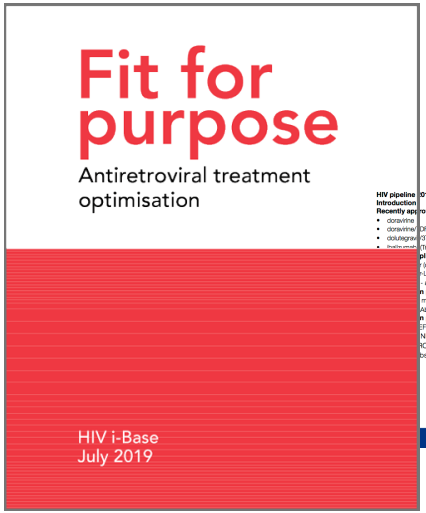
i-Base pipeline reports: updated twice a year

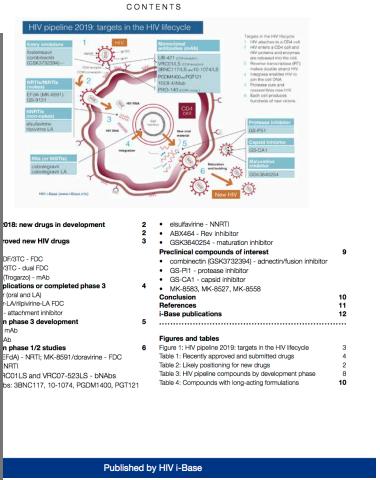
Review of new HIV drugs in development.

Part of Fit For Purpose: treatment optimisation (and paediatric pipeline).

http://i-base.info/fit-for-purpose

Produced for CROI and IAS.





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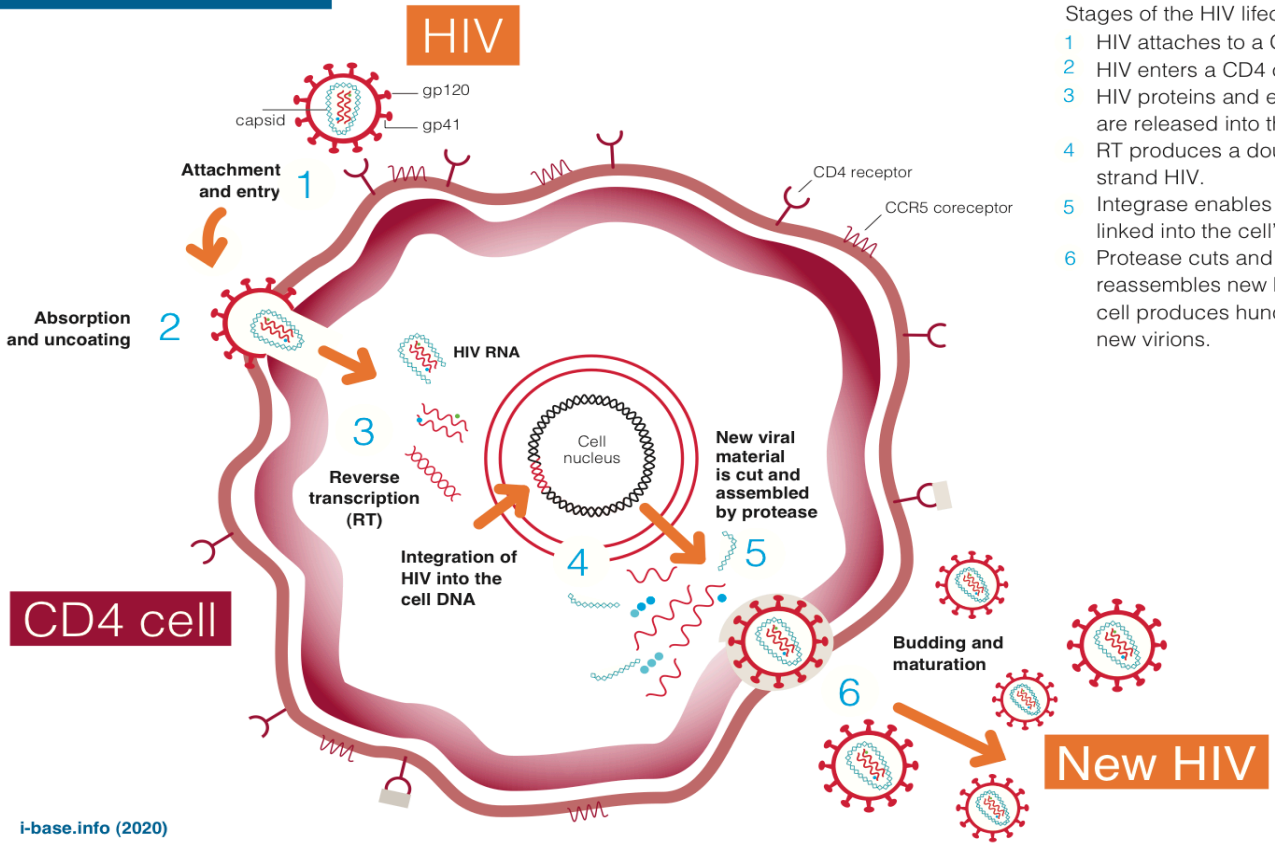
The HIV lifecycle



Stages of the HIV lifecycle

1. HIV attaches to a CD4 cell.
2. HIV enters a CD4 cell.
3. HIV proteins and enzymes are released into the cell.
4. RT produces a double strand HIV.
5. Integrase enables HIV to be linked into the cell's DNA.
6. Protease cuts and reassembles new HIV. Each cell produces hundreds of new virions.

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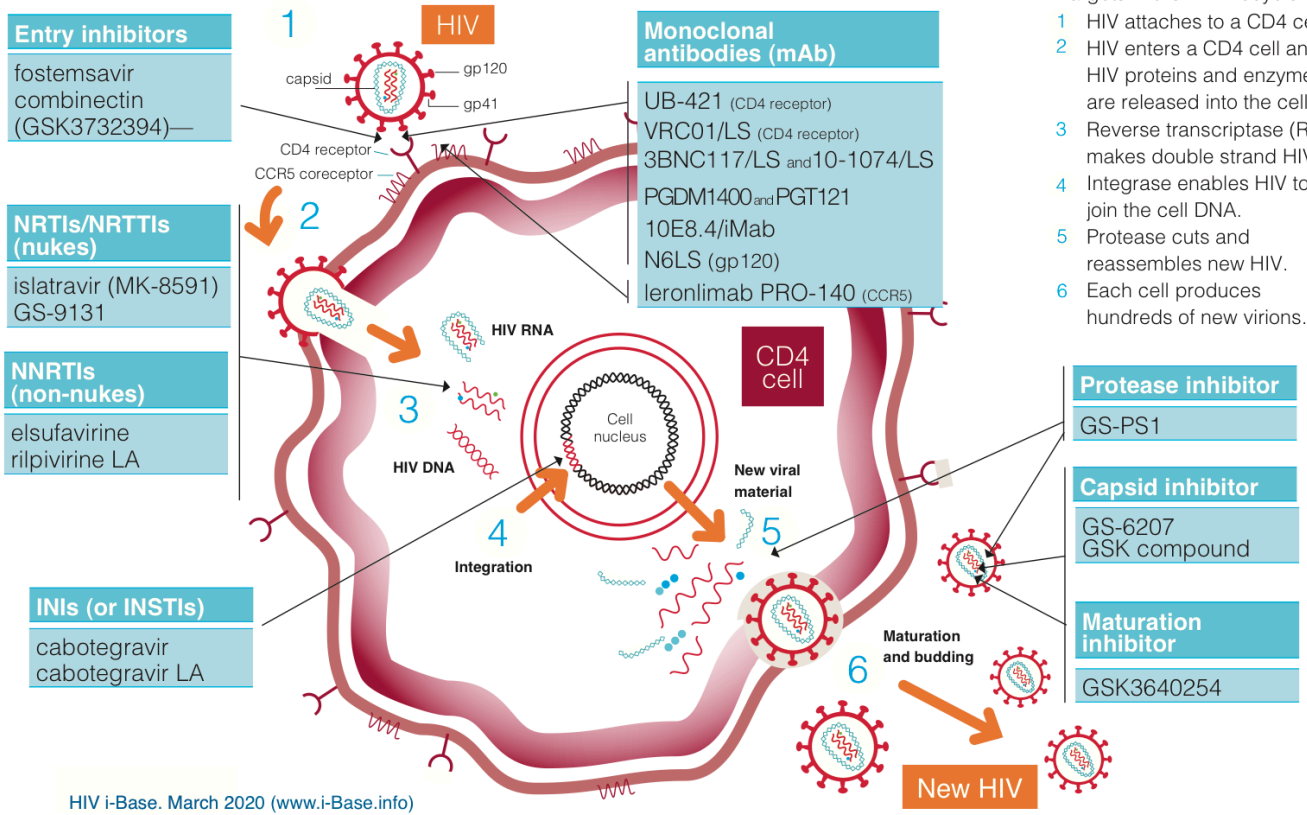
HIV pipeline 2020: targets in the HIV lifecycle



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. Each cell produces hundreds of new virions.

HIV i-Base. March 2020 (www.i-Base.info)

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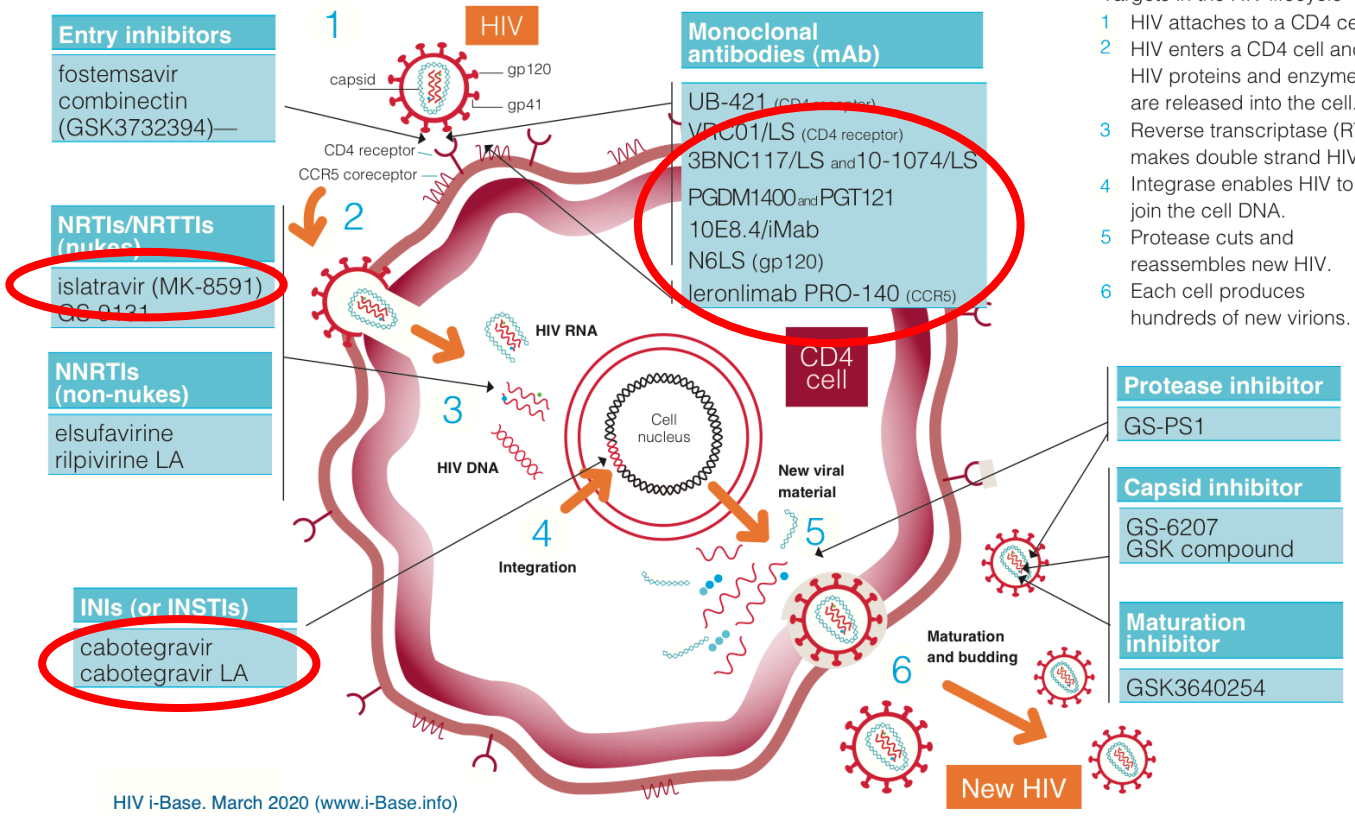
HIV pipeline 2020: targets in the HIV lifecycle



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PrEP pipeline: update (+ RIO study)

- **cabotegravir** long acting injections: CAB LA
- **islatravir** - oral monthly - annual implant
- bNAbs - **VRC01 AMP study** and long-acting LS formulations
- Other approaches: microbicides, vaccines, single and multi-compound vaginal rings, patches, suppositories, nano-films, douche solutions, vaginal and rectal gels, soft implants etc
- Research challenges and ethics
- Dual long-acting bNAbs - **RIO study** – (UK cure-related)

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Current oral PrEP

- **TDF/FTC –** daily or on-demand depending on population/risk
- **F/TAF –** non-inferior to TDF/FTC – more flexible for missed doses.

Close to 100% efficacy when adherence is good. Few side effects.

High level of adherence needed for daily PrEP – only option for women and trans men and women.

Easy to miss ‘pre’ dose with on-demand dosing

Price of generic vs new formulations

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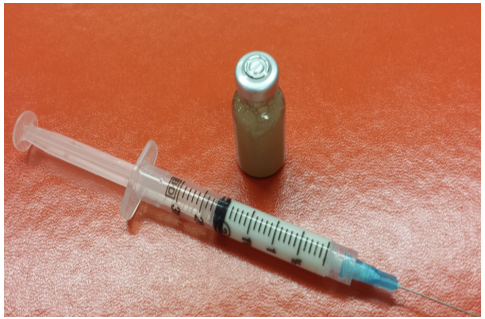
cabotegravir long-acting (CAB-LA)



- integrase inhibitor: one month of daily oral pills, then IM (into muscle) injections – every 8 weeks

- very long half-life – drug levels still detectable at least one year after a single injection – but up to 2.5 years in men and 3.5 years in women.

- studies mandate daily oral PrEP to cover the PK tail
  - otherwise HIV infections will develop drug resistance
  - but in practice?

- regulatory update for treatment: Dec 2019 – delay with FDA letter about scale manufacturing problems (not safety or efficacy)

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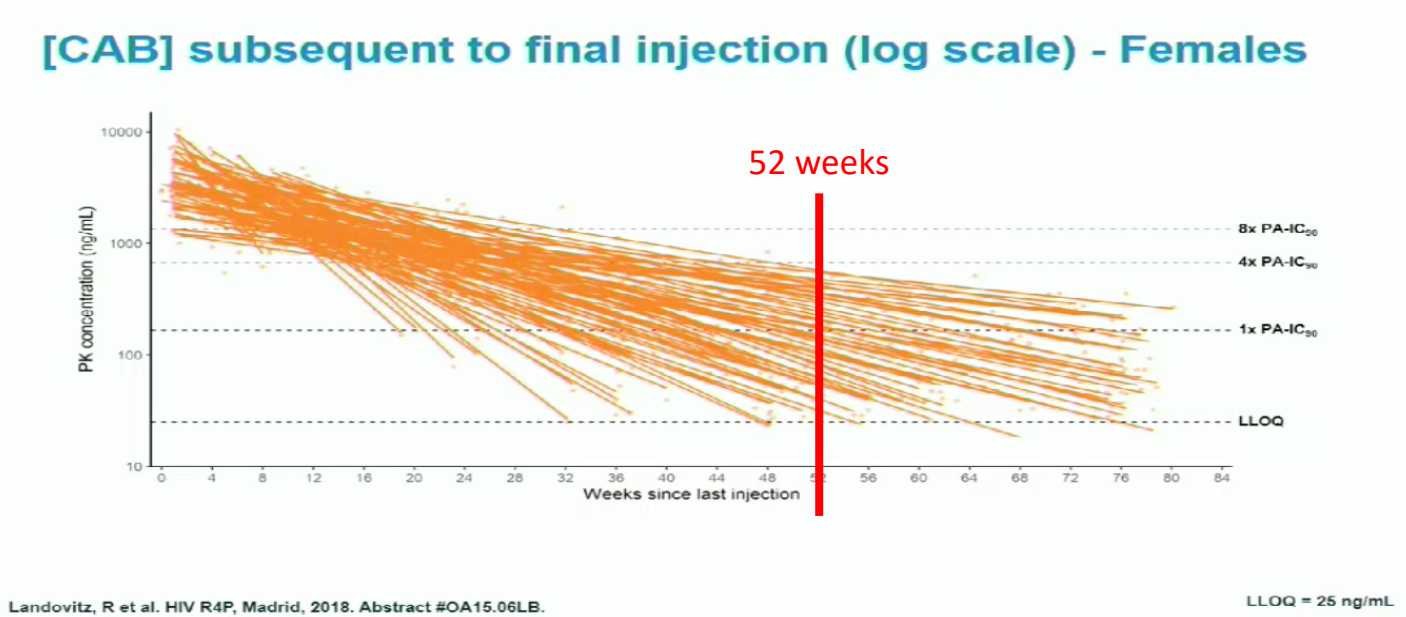
The ‘tail’: cabotegravir long-acting (CAB-LA)



- very long PK tail – catching HIV during the tail = drug resistance.

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Ongoing cabotegravir PrEP studies

Two public funded (NIAID) studies - similar designs in different populations.

Randomised, placebo controlled phase 2b/3 studies - CAB LA vs daily oral TDF/FTC (+ placebos); Both due to end 2022.

- HPTN 083 - n=5000 trans women and gay men - US, South America, Thailand, Vietnam, South Africa.

- HTPN 084 - n=3200 women in seven high incidence African countries: Botswana, Kenya, Malawi, South Africa, Swaziland, Uganda, Zimbabwe.

Practical issues for adherence, stopping PrEP and price.

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islatravir (EFdA)

NRTTI - similar to nukes – acquired by Merck in 2012.

Derivative of flavouring in soy sauce (Yasama corporation).

Highly potent against HIV – tiny daily treatment dose 0.75 mg

Two formulations proposed for PrEP for unmet need:

i) annual implant (64 mg).

ii) once-monthly pill - 12 pills a year – an option for all sexually active people? All women? etc

Hormonal contraceptive implant (Nexplanon)

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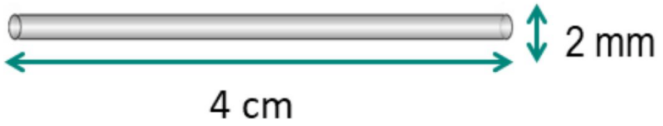
islatravir (EFdA)



All dependent on showing similar efficacy to current oral PrEP.

Current PrEP study:

MK-8591-016 - Phase 2 –
n=250 - safety, tolerability, PK
of monthly 60 mg and 120 mg pill in HIV negative people at low risk of HIV -

12 vs 365 pills a year. Due to end Dec 2020.

bNAbs *(pronounced: bee-nabs)*

- broadly Neutralising monoclonal Antibodies
- Generated from HIV-positive people who develop strong antibodies to HIV (after several years).
- Been known since early HIV research but only recently isolated and cloned for use as treatment.
- Need to use in combination – some trispecific.
- Many other treatments – cancer, immune disorders.
- Priced as very expensive drugs: £5K - >£200,000/year.

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HIV bNAbs

- Two mechanisms:
  - direct antiretroviral (entry inhibitors)
  (can have ~1.5 log mono, 2 log dual on VL
  - immune modulating vaccine-type effect (after drug levels have left)

- Long acting LS formulations (ie from M428L and N434S) extends half life x 4 – allows 6-monthly dosing.

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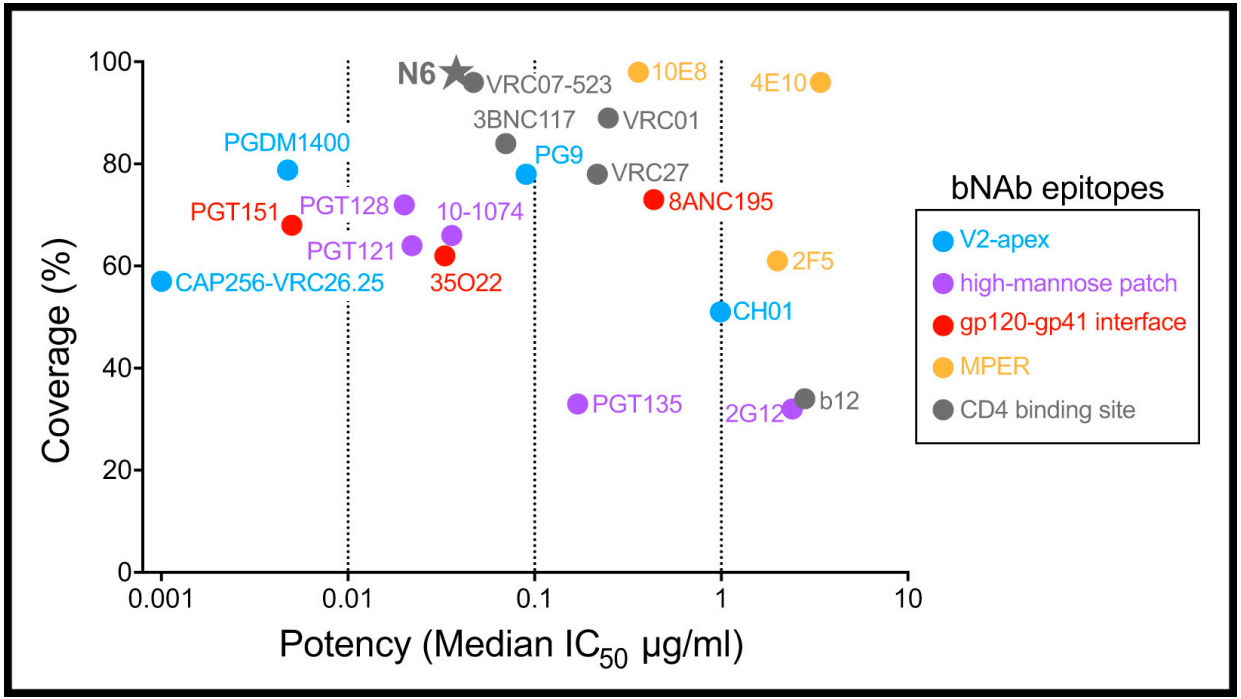
Breadth vs potency of HIV bNAbs



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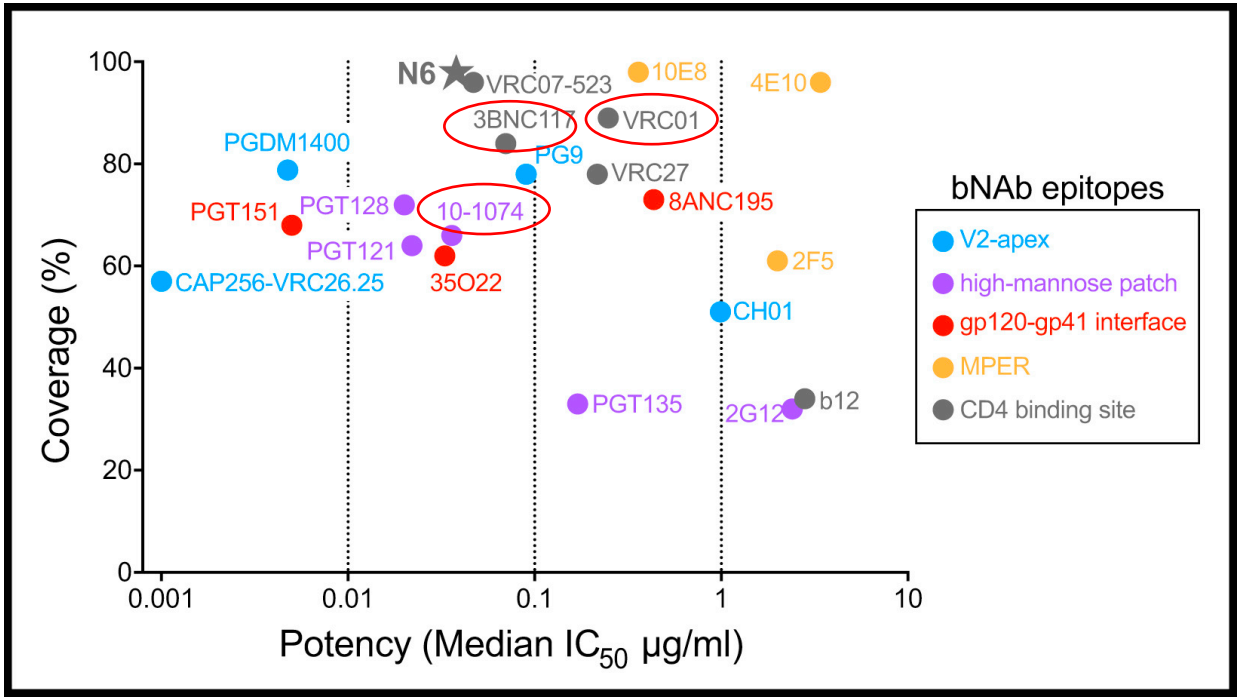
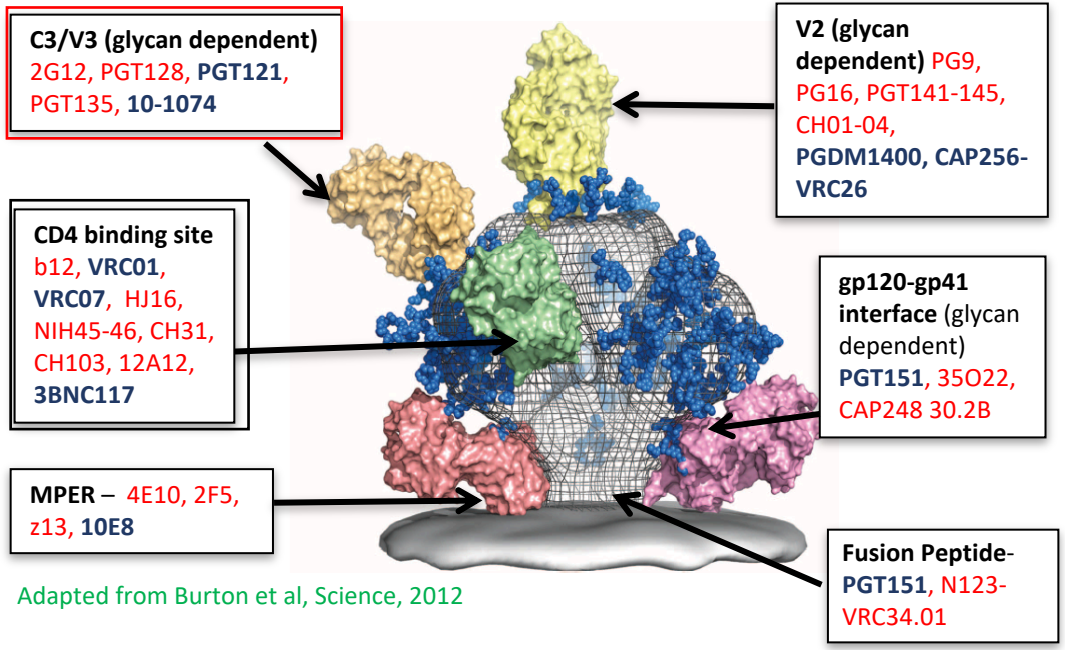


bNAb binding on HIV envelope glycoprotein:
different target sites will reduce cross-resistance



Adapted from Burton et al, Science, 2012

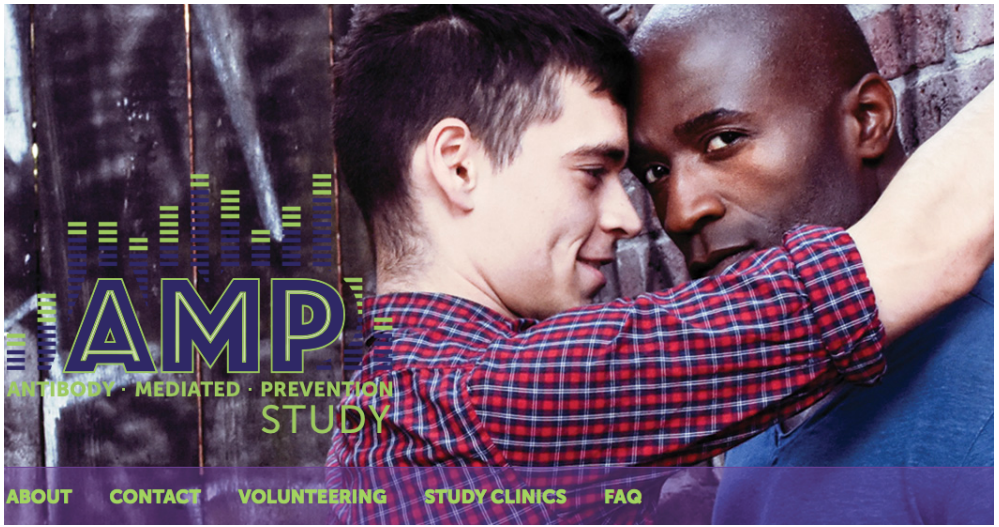
AMP studies: VRC01

Two phase 2b/3 studies: started 2015 - results end 2020

- infusion every 8 weeks vs placebo.
- large international randomised, placebo-controlled phase 2b NIAID studies:

i) n=2700 men and transgender (TG) persons who have sex with men in North America South America and Switzerland. Some oral PREP allowed.

ii) n=1900 women in seven sub-Saharan African countries. No oral PrEP



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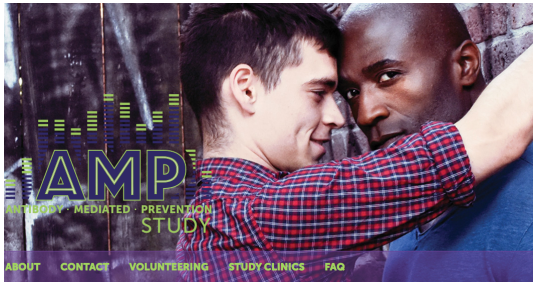
AMP studies: VRC01

Controversies:

- Low expectation of benefit.
- Placebo design
- Single Ab – monotherapy
- Risk of resistance
- Clade coverage for African countries?
- Didn't use long-acting LS version
- Results expected – by end 2020



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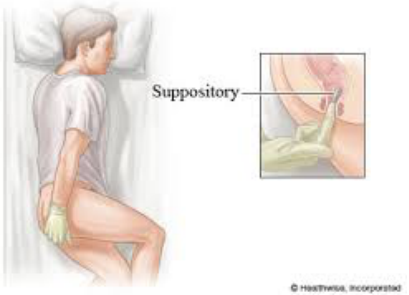
Other approaches to HIV prevention

i) Microbicides – gels or vaginal rings (tenofovir, dapivirine: with potential to coformulate rings with hormonal contraceptives or STI treatments etc). Technology to individualise ring size, shape, colour etc.

ii) HIV vaccines:

- HVTN 702 - just ended (Feb 2020) early due to no efficacy
- HVTN 705 - Phase 3 studies ongoing - IMBOKODO - in 2600 women in SSA and MOSAICO in 3800 MSM and transgender.

iii) Alternative PrEP formulations – ie for TDF – implants, slow release formulations, vaginal and rectal gels, films (dissolve on tongue), douche products etc



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Research and ethical challenges

How to show efficacy of new promising PrEP compounds?

- Few HIV infections in DISCOVER study: 7 vs 15 in 5300 pts
- Reduced HIV incidence in many countries due to U=U, PrEP, earlier testing, earlier treatment etc
- Ethics of providing standard of care for prevention for all participants - ie oral PrEP rather than placebo studies.
- Can indicator infections be used as a surrogate marker? rectal STIs etc
- Or take new PrEP to populations/countries with high HIV incidence.

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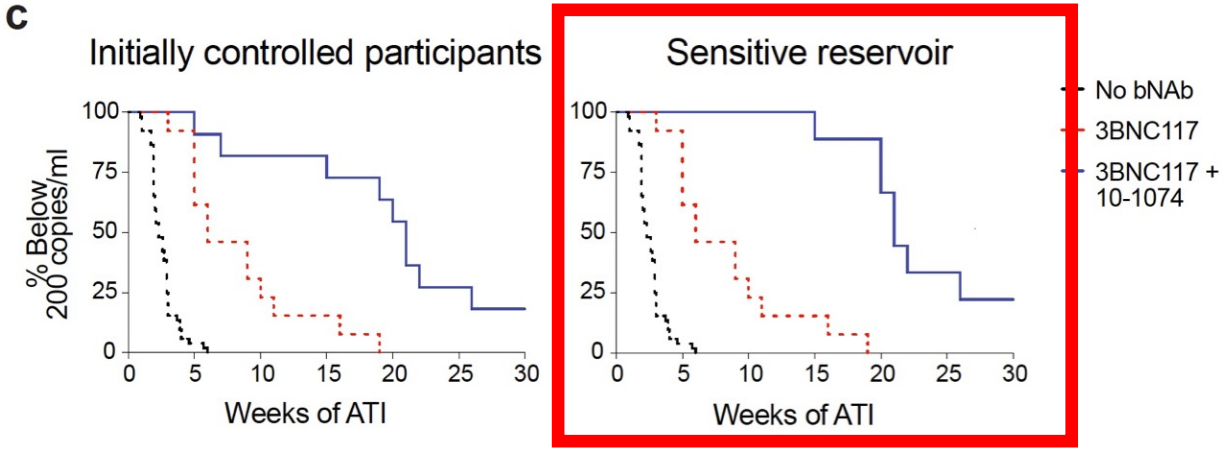
Cure-related research: dual bNAbs stopped viral rebound……



- Viral suppression for 5 to >30 weeks: 3BNC117 an 10-1074 (now Gilead)
- Median time to rebound 21 weeks vs 2.3 weeks for ART-only controls vs 6-10 weeks for single bNAb.
- 2/13 people did not rebound for a year (now one > 24 months)
- Rebound in others due to resistance or as bNAb concentration dropped.

The RIO Trial: Dual long-acting bNAbs in treated Primary HIV Infection**.**

Randomised, placebo controlled, dual long-acting bNAbs
N=75 HIV+ treated in early infection.
BNC117-LS and 10-1074-LS. Randomised, placebo controlled.
Stop ART and measure time to viral rebound.
Placebo arm roll-over to active bNAbs.
Easy access to PEP and PrEP included for HIV negative partners

Summary and conclusions

- Oral PrEP already 100% effective – but not an option for many people.
- Some results by end 2020: islatravir monthly pill (phase 2)
  AMP studies VRC01 (phase 3)
- Other formulations and compounds are being studied.
- PrEP efficacy is increasingly difficult to study – research needs to be in people with greatest need (ie at highest risk). Maybe not in high income countries.
- Access once approved is essential – relative to cost of a pint and a packet of condoms – ie current generic PrEP.

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Thanks:

Polly Clayden, Roy Trevelion: i-Base

Sarah Fidler, John Frater: RIO study

Questions ☺

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Back-up slides

Current ART

- There are now 10 single-pill, once-daily, fixed dose combinations (FDCs).
- Highly effective (>95% get undetectable viral load – especially using unboosted integrase inhibitor-based ART).
- Life expectancy is close to HIV negative – if diagnosed early with access to early ART.
- But better treatment – and a cure – is still seen as an achievable scientific and commercial goal

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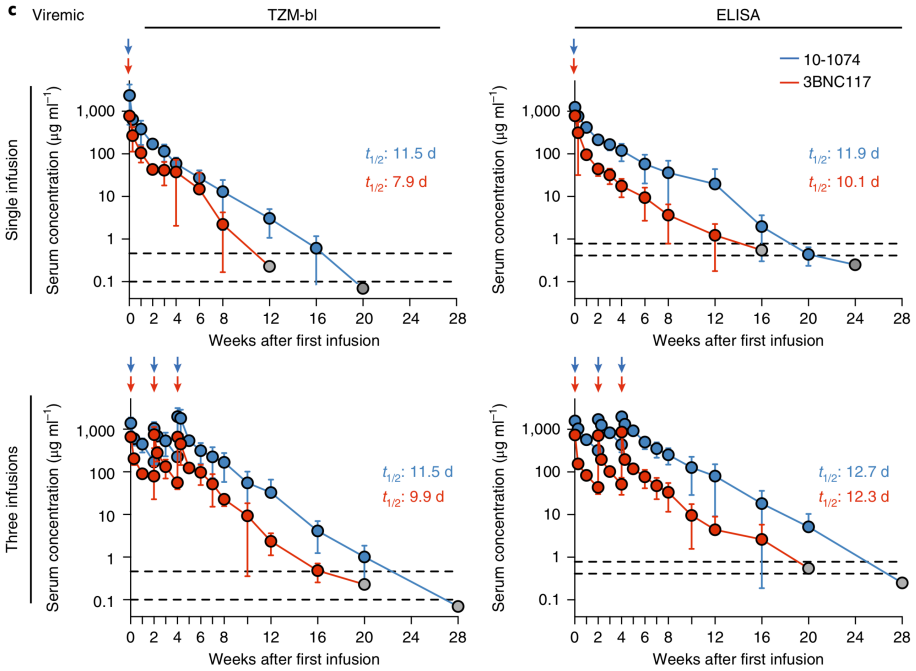
Why these bNAbs

Combined bNab 3BNC117 + 10-1074 act as antivirals in viraemic patients to reduce HIV Viral load by 2.5 log



Bar-On et al Nature Medicine 2018 Sept. 10 1038

Risk	Risk management and mitigation
Risk of bNab administration	Anaphylaxis (none reported) Mild local or systemic reactions to infusion Clot formation (checked at screening)
Risk of ATI	Drop in CD4 count (frequent monitoring) eligibility criteria exclude low nadir or current CD4 count Symptoms of viral rebound Exclude any co-morbidity and co-infections, previous malignancy, OI, or CVA MI ART resistance (only interrupt on bPI or INSTI avoid NNRTI
Risk of onward viral transmission	Access to PrEP services to any HIV-negative partners Condoms Pregnancy prevention for duration of study for women participants