COVID-19 & Treatment Update

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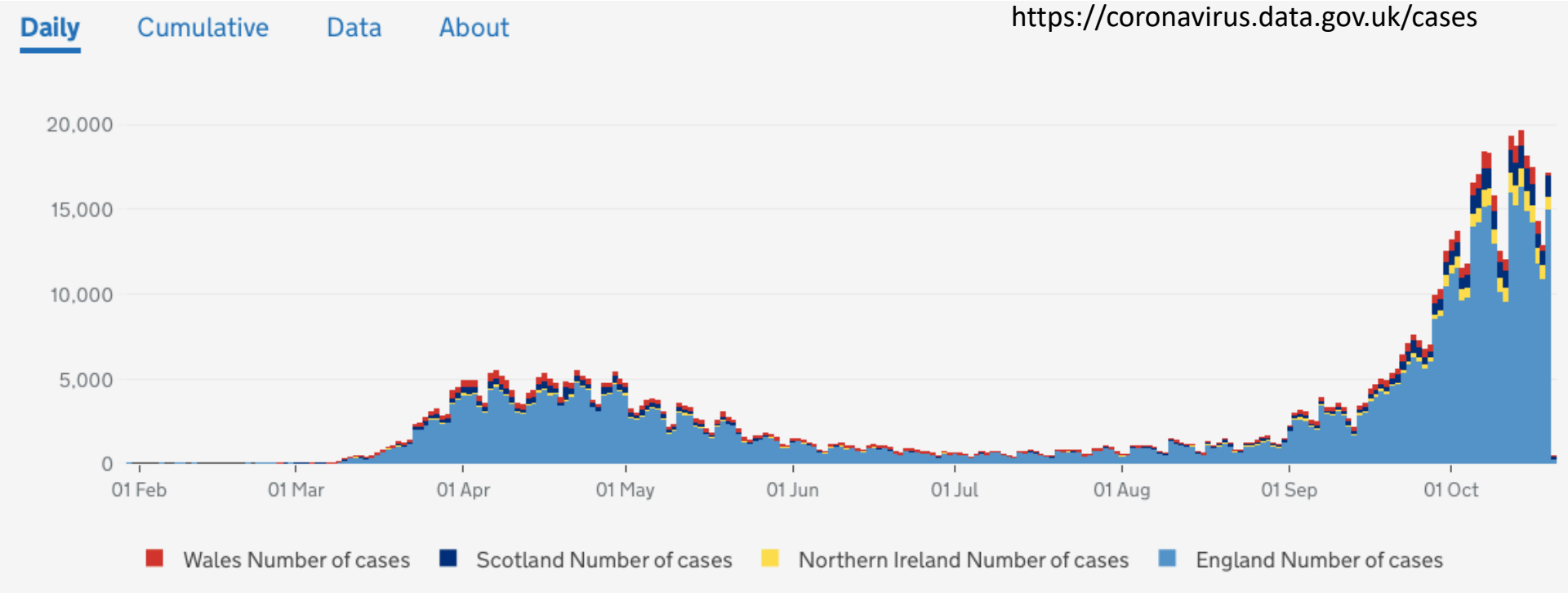
Positive East
21 October 2020

COVID-19: London

- Second wave is now established (as predicted months ago)
- Same virus as in April – will have same outcomes
- Better experience in hospital but no breakthrough in treatment.
  - remdesivir if hospitalised and used early
  - dexamethasone – if severe (on oxygen or intubated)
- Please follow all precautions: hygiene, distancing etc
- Vaccine will not be available this year, maybe not for six months, even if lucky. First vaccine unlikely to be the best.

COVID-19: daily cases

https://coronavirus.data.gov.uk/cases



COVID-19: HIV

- Being HIV positive doesn't seem to have a big impact on risk of having COVID-19, or of having more severe outcomes.
- But other COVID factors do – and these are common for many of us: high blood pressure, diabetes, lung complications (asthma, COPD), kidney disease, being overweight.
- Ethnicity/race: BAME communities more affected.
- More vulnerable if CD4 is very low (under 50), chemotherapy, transplant recipients etc. With these continuing to shield is recommended.

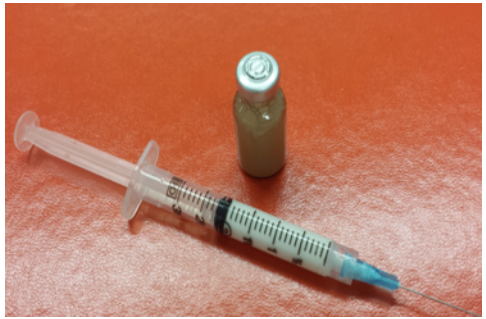
HIV news

- Modern drugs – increasingly easy and effective – but weight gain recognised with dolutegravir, likely bictegravir and TAF. Higher risk in women and if African.
- Injections – just approved in EU – access might take another year in the UK.
- Long-acting drugs in development - maybe every 6 months - but 4-5 years away.
- PrEP options (and PEP) – perhaps monthly pill, annual implant etc

PrEP pipeline: update

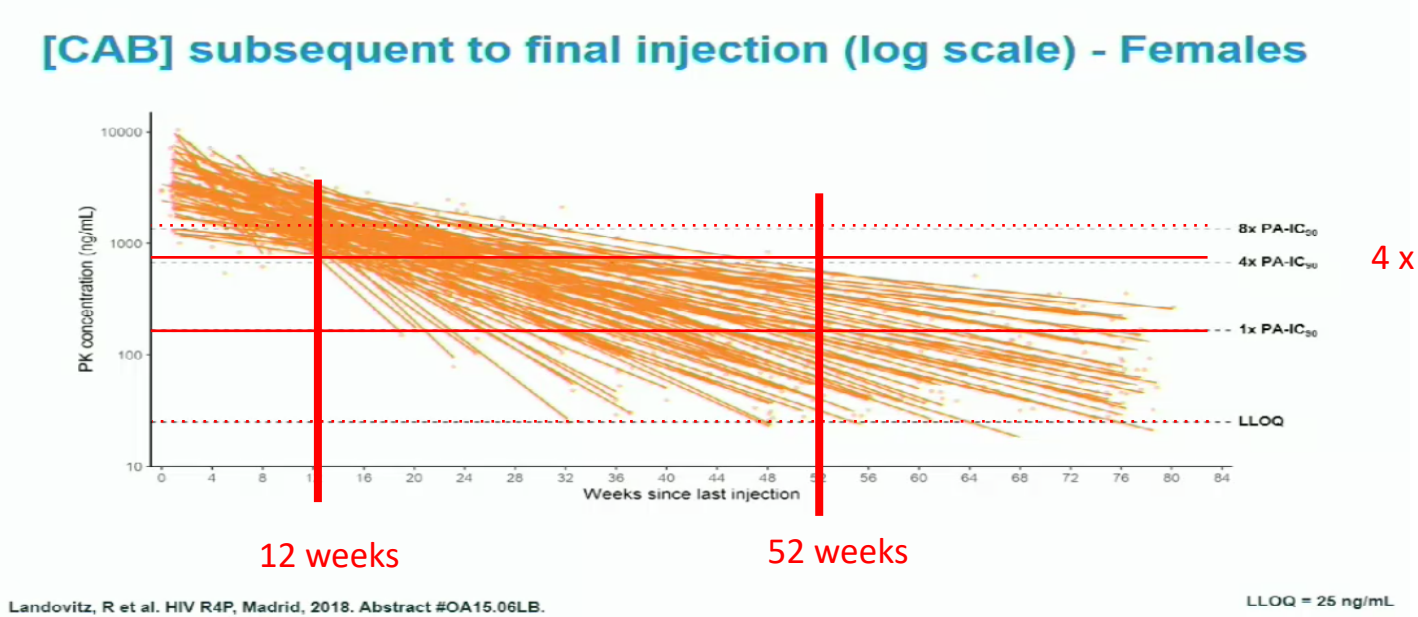
- **cabotegravir** long acting injections: CAB LA
- **islatravir** – oral (daily, weekly, monthly) - annual implant
- bNAbs - **VRC01 AMP study** and long-acting LS formulations
- Microbicides, single and multi-compound vaginal rings, patches, suppositories, nano-films, douche solutions, vaginal and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

Injectable PrEP (CAB-LA)



- Cabotegravir 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 require daily oral PrEP to cover the PK tail
  - otherwise HIV infections will develop drug resistance
  - but in practice?
- Recently resubmitted to the US FDA for treatment based on monthly dosing. Might be able to be given every two months.

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



4 x PA IC50

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

Injectable PrEP: interpreting results

AIDS 2020 23RD INTERNATIONAL AIDS CONFERENCE 6-10 JULY 2020

- Statistical superiority – important – but likely due to lower adherence to pills. – especially over time.

- TDF/FTC is 99.99% effective **with good adherence** – 60% better is not the best way to explain the results.

- Results show importance of choice for PrEP.

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

Treatment include daily and weekly versions.

Hormonal contraceptive implant (Nexplanon)

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.

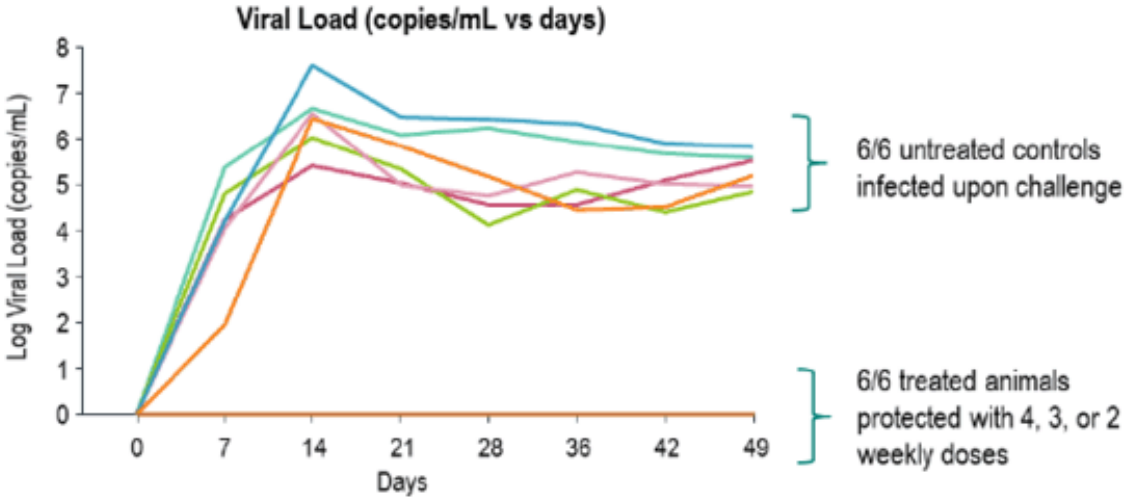
Islatravir: CROI 2020

- 12 rhesus macaques were challenged rectally with high dose SHIV.
- 24 hours later, half received a total of 4 weekly doses of islatravir (3.9 mg/kg) and half were untreated controls.
- Follow-up for 7 weeks then step down to 3, then 2 weekly doses.
- After the single dose, 4/6 animals were still protected, but 2/6 became viraemic (at days 14 and 49).

Markovitz M et al. CROI 2020.

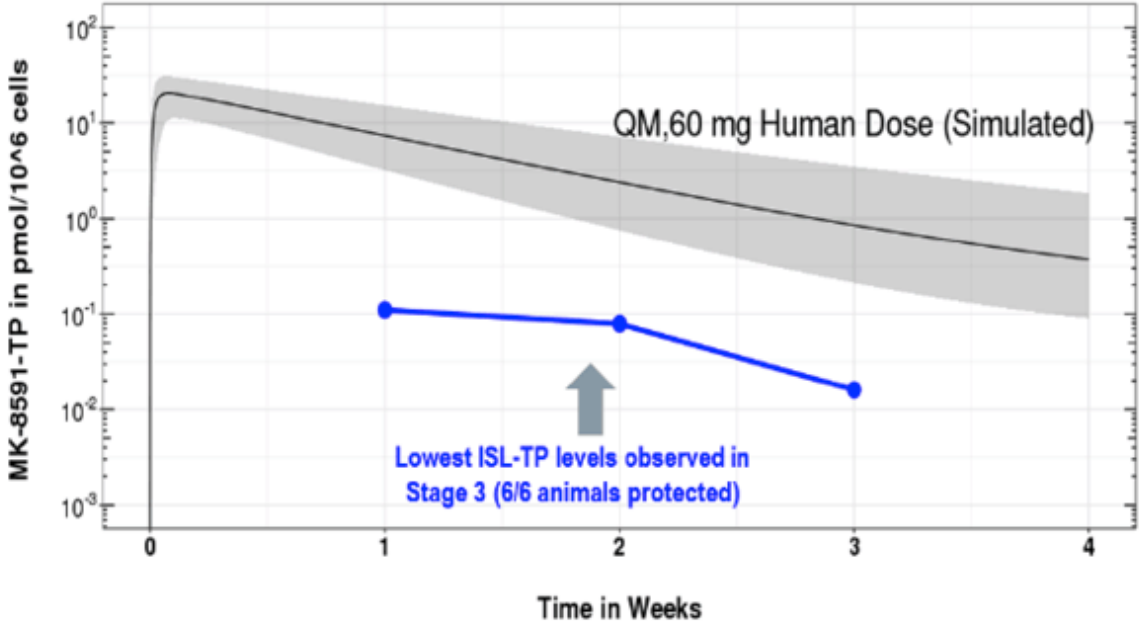
Islatravir: CROI 2020

ISL Provides Complete Protection Against Infection When Administered 24 Hours After Challenge With Two or More Weekly Doses



Islatravir: CROI 2020

Single Oral Doses of ISL Given Within 24 Hours of Infection May Provide an Effective PEP Option in Humans



bNAbs

- 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.

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.

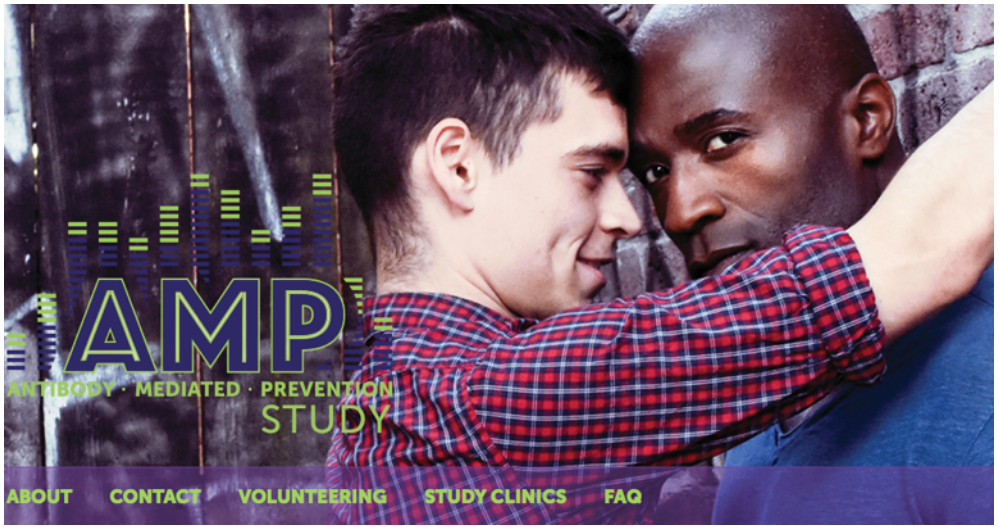
AMP studies: VRC01

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.

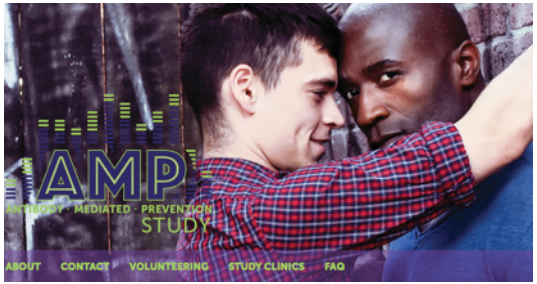
ii) n=1900 women in seven sub-Saharan African countries. No oral PrEP



AMP studies: VRC01

Controversies:

- Not expected to have 100% effect.
- 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



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.
Dapivirine just approved by EU – but for use outside the EU.

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

Vaginal rings

3D printing can individualise rings – size, shape, colour, and use multiple compounds – PrEP, antibiotics, contraceptive etc

Benhabbour SRet al. R4P2018, 21-25 October 2018. Oral abstract OA08.06. Audio webcast. http://webcasts.hivr4p.org/console/player/40471

Carbon 3D Inc
https://www.carbon3d.com

Vaginal rings: EU decision on dapivirine

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Vaginal ring to reduce the risk of HIV infection for women in non-EU countries with high disease burden

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News 24/07/2020

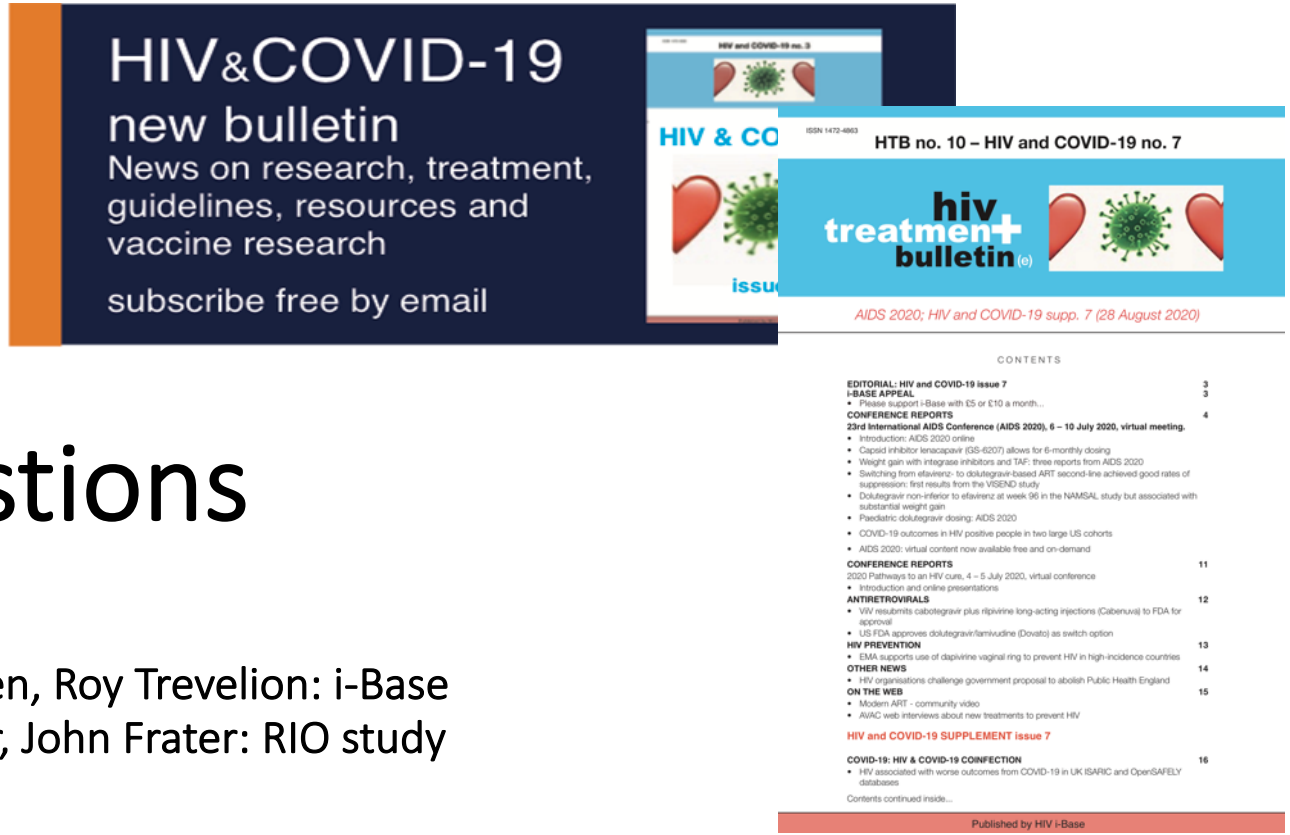
EMA's human medicines committee (CHMP) has adopted a positive opinion for Dapivirine Vaginal Ring (dapivirine) used to reduce the risk of infection with the human immunodeficiency virus type 1 (HIV-1), in combination with safer sex practices when oral pre-exposure prophylaxis (PrEP) is not used, cannot be used or

In Memory: Timothy Ray Brown, the Berlin patient, the first person to be cured of HIV

Activist for PrEP, U=U and an HIV cure.

https://i-base.info/htb/39020

Timothy Ray Brown, filmed at the International AIDS Conference in 2015 for 'Is a cure for HIV possible'. (28 July 2015). https://www.youtube.com/watch?v=IJgKYybd2aI



Questions

Thanks:
Polly Clayden, Roy Trevelion: i-Base
Sarah Fidler, John Frater: RIO study

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.

Back-up slides

HTPN 083 results – July 2020

- Late breaker results reported at AIDS 2020.
- Prespecified: 50% of participants <30 years old, 10% transgender women (TGW) and >50% of US participants would be black/African-American.

- Cabotegravir was statistically superior compared to TDF/FTC: 13 vs 39 people became HIV positive (HR: 0.34; 95%CI: 0.18 to 0.62, p=0.0005).
- Both arms were highly effective: low adherence likely to explain new infections in the TDF/TFC arm.

- 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.

Landovitz R et al. Late breaker oral abstract OAXLB0101.

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 were due to end 2022.

- HPTN 083 - n=5000 gay men & trans women - US, South America, Thailand, Vietnam, South Africa. Results reported at AIDS 2020 – positive results seen earlier than expected.

- 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.

Oral PrEP: F/TAF

- **F/TAF –** non-inferior to TDF/FTC – US 2019.

Effectively 100% protection with good adherence.

Smaller tablet. Less risk of renal and bone complications.

Better PK for late/missed dosing but no data for on-demand (2:1:1) or in women

Significantly more expensive compared to generic TDF/FTC

Current oral PrEP: TDF/FTC

- **TDF/FTC –** daily or on-demand (2:1:1) for some people.

Approved: US 2012, EU 2015, Scotland 2017 and England 2020.

Effectively 100% protection with good adherence.

Inexpensive (~£17 for 30 tablets). ~£2.50 per on-demand cover.

Few side effects. Maybe caution with bone health if young.

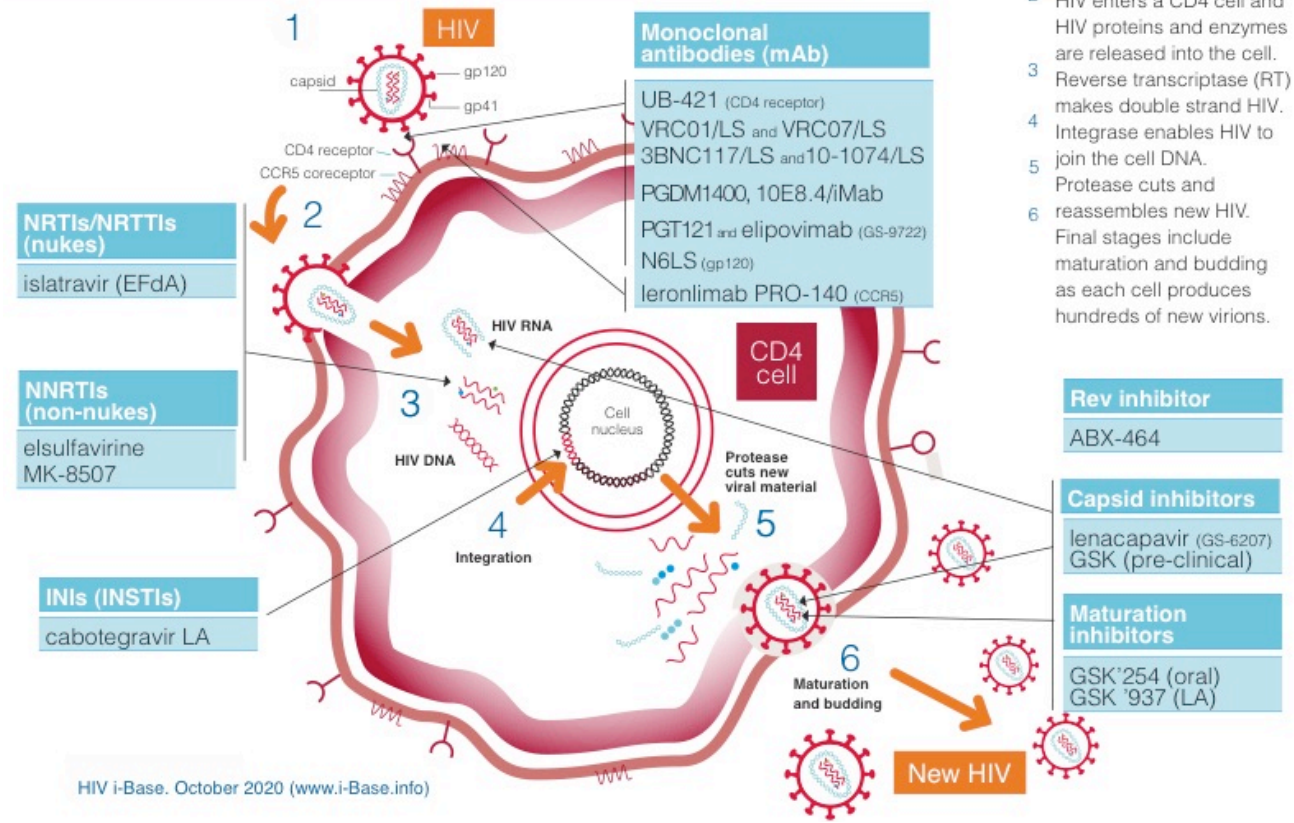
High level of adherence needed for daily PrEP. Only option for women and trans men and women: need 6 or more daily pills a week.
Easy to miss 'pre' dose with on-demand dosing

Advances in HIV treatment

- 1981 – 1987: from no treatment to AZT. Time to 3TC?
- 1987 – 1997: from mono to triple HAART (ART) - 3-drug combination therapy. Life-saving - but, multiple pills often >20/day, difficult side effects.
- 1997 – 2007: better, easier treatment – single pill FDC Atripla.
- 2007 – 2017: 10 single-pill, once-daily, fixed dose combinations (FDCs)
  Swiss Statement, PrEP, PARTNER studies and U=U.
  START study in 2015 supported universal ART.

Next decade? Long-acting alternatives to daily oral ART – potential for treatment every six months by 2027? - and a cure?

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. Final stages include maturation and budding as each cell produces hundreds of new virions.

Key: INSTI: integrase strand transfer inhibitor; LA: long-acting; mAb: monoclonal antibody; NRTI: nucleoside/tide reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor.