LANCET HIV (JULY 2018- FEBRUARY 2019)

IMPACT FACTOR: 9.842

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"I would like to acknowledge the Gadigal of the Eora Nation, the traditional custodians of this land and pay my respects to the Elders both past and present."

Articles

- 9 Short article reviews
- 1 Editorial review
- 1 Main article review

Population-level effectiveness of rapid, targeted, high-coverage roll-out of HIV pre-exposure prophylaxis in men who have sex with men: the EPIC-NSW prospective cohort study
Implementation in Communities New South Wales (EPIC-NSW) research group

- HIV PrEP is highly effective in MSM at the individual level, but data on population-level impact are lacking.
- Rapid, targeted, and high coverage roll-out of PrEP in an MSM epidemic would reduce HIV incidence in the cohort prescribed PrEP and statewide in Australia's most populous state, New South Wales.
- Methods
  - The Expanded PrEP Implementation in Communities–New South Wales (EPIC-NSW) study is an implementation cohort study of daily co-formulated tenofovir disoproxil fumarate and emtricitabine as HIV PrEP.
  - Recruited high-risk gay men in a New South Wales-wide network of 21 clinics.
  - Reported protocol-specified co primary outcomes at 12 months after recruitment of the first 3700 participants: within-cohort HIV incidence; and change in population HIV diagnoses in New South Wales between the 12-month periods before and after PrEP rollout.

Andrew E Grulich et al; HIV Lancet Issue: Volume 5, Nov 2018, p e629- e637

Population-level effectiveness of rapid, targeted, high-coverage roll-out of HIV pre-exposure prophylaxis in men who have sex with men: the EPIC-NSW prospective cohort study

Implementation in Communities New South Wales (EPIC-NSW) research group

- Findings
  - 3700 participants in the 8 months between March 1, 2016, and Oct 31, 2016.
  - 99% were men, 96% identified as gay, and 4% as bisexual.
  - Median age was 36 years (IQR 30–45 years).
  - 3069 (83%) participants attended a visit at 12 months or later.
  - HIV diagnoses in MSM in New South Wales declined from 295 in the 12 months before PrEP roll-out to 221 in the 12 months after (relative risk reduction [RRR] 25·1%, 95% CI 10·5–37·4).
  - There was a decline both in recent HIV infections (from 149 to 102, RRR 31·5%, 95% CI 11·3 to 47·3) and in other HIV diagnoses (from 146 to 119, RRR 18·5%, 95% CI –4·5 to 36·6).
- Interpretation
  - PrEP implementation is effective to reduce new HIV infections at the population level.
- Funding Gilead Sciences.

Andrew E Grulich et al; HIV Lancet Issue: Volume 5, Nov 2018, p e629- e637

Community-level changes in condom use and uptake of HIV PrEP by gay and bisexual men in Melbourne and Sydney, Australia : results of repeated behavioural surveillance in 2013-2017

- Pre-exposure prophylaxis (PrEP) has been rapidly rolled out in large, publicly funded implementation projects in Victoria and New South Wales, Australia.
- Using behavioural surveillance of gay and bisexual men, analysed the uptake and effect of PrEP, particularly on condom use by gay and bisexual men not using PrEP.
- Methods
  - Data was collected from the Melbourne and Sydney Gay Community Periodic Surveys (GCPS), cross-sectional surveys of adult gay and bisexual men in Melbourne, VIC, and Sydney, NSW.
  - Recruitment occurred at gay venues or events and online.
  - Eligible participants were 18 years or older (face-to-face recruitment) or 16 years or older (online recruitment), identified as male (including transgender participants who identified as male); and having had sex with a man in the past 5 years or identified as gay or bisexual, or both.
  - Using multivariate logistic regression, they assessed trends in condom use, condomless anal intercourse with casual partners (CAIC), and PrEP use by gay and bisexualmen, controlling for sample variation over time.

Martin Holt et al HIV Lancet Issue: Volume 5, August 2018, p e448-456

Community-level changes in condom use and uptake of HIV PrEP by gay and bisexual men in Melbourne and Sydney, Australia : results of repeated behavioural surveillance in 2013-2017

Findings

- Between Jan 1, 2013, and March 31, 2017, 27 011 participants completed questionnaires in the Melbourne (n=13 051) and Sydney (n=13 960) GCPS.
- In 2013, 1% of 2692 men reported CAIC and were HIV-negative and using PrEP compared with 5% of 3660 men in 2016 and 16% of 4018 men in 2017 ($p<0{\cdot}0001$).
- Consistent condom use was reported by 46% of 2692 men in 2013, 42% of 3660 men in 2016, and 31% of 4018 men in 2017 ($p<0{\cdot}0001$).
- In 2013, 30% of 2692 men who were HIV-negative or untested and not on PrEP reported CAIC, compared with 31% of 3660 men in 2016, and 29% of 4018 in 2017 (non-significant trend).

- Interpretation
  - A rapid increase in PrEP use by gay and bisexual men in Melbourne and Sydney was accompanied by an equally rapid decrease in consistent condom use.
- Funding Australian Government Department of Health, Victorian Department of health and Human Sciences and NSW Ministry of health

Martin Holt et al HIV Lancet Issue: Volume 5, August 2018, p e448-456

Acquisition of tenofovir-susceptible, emtricitabine-resistant HIV despite high adherence to daily pre-exposure prophylaxis: A case report

- Pre-exposure prophylaxis (PrEP) with emtricitabine and tenofovir disoproxil fumarate is highly protective against HIV infection. A case of tenofovir-susceptible, emtricitabine-resistant HIV acquisition despite high adherence to daily PrEP.
- Methods
  - Adherence to PrEP was assessed by measuring concentrations of emtricitabine and tenofovir disoproxil fumarate or their metabolites in plasma, dried blood spots, and hair.
  - After seroconversion, genotypic and phenotypic resistance of the acquired virus was determined by standard clinical tests and by single-genome sequencing of proviral genomes.

Stephanie E Cohen et al, LANCET HIV Issue: Volume 6, Jan 2019,p e43-50

Acquisition of tenofovir-susceptible, emtricitabine-resistant HIV despite high adherence to daily pre-exposure prophylaxis: A case report

- Findings
  - A 21-year-old Latino man tested positive for HIV infection 13 months after PrEP initiation.
  - He had a negative HIV antibody test, but detectable HIV RNA with 559 copies per mL.
  - He reported good adherence to daily PrEP.
  - Segmental hair analysis, dried blood spot and plasma levels confirmed adherence
  - The HIV genotype revealed Met184Val, Leu74Val, Leu100Ile, and Lys103Asn mutations in reverse transcriptase, and the phenotype showed susceptibility to tenofovir disoproxil fumarate and resistance to emtricitabine.
- Interpretation
  - Quarterly screening for HIV and STI facilitates early diagnosis in people on PrEP combined with prompt linkage to care and partner services this can prevent onward transmission of HIV.
- Funding US National Institutes of Health.

Stephanie E Cohen et al, LANCET HIV Issue: Volume 6, Jan 2019,p e43-50

HIV incidence in Indigenous and non-Indigenous populations in Australia: a population-level observational study

- Australia has set a national target of ending HIV by 2020.
- Methods
  - Using the National HIV Registry at The Kirby Institute at UNSW, Sydney, NSW, Australia,
  - Annual HIV notification data for 1996–2015.
  - Patients who were not born in Australia were excluded.
  - Calculated the rates of HIV diagnoses with annual trends in notification rates for Indigenous versus non-Indigenous Australians by demographic characteristics, exposure categories, and stage of HIV at diagnosis.
  - Annual rate ratio (RR) and 4 year summary rate ratio (SRR) trends were calculated to determine patterns of HIV diagnosis in the two populations.

James Ward et al, HIV LANCET Volume 5,September 2018,p e506-514

HIV incidence in Indigenous and non-Indigenous populations in Australia: a population-level observational study

- Findings
  - Jan 1, 1996, and Dec 31, 2015.
  - 11 492 people born in Australia were reported with a diagnosis of HIV, of whom 4% were recorded as Indigenous Australians and the remaining 96% as non- Indigenous Australians.
  - For exposure to HIV, among Indigenous Australians a higher proportion of diagnoses occurred among women, and through injecting drug use and heterosexual sex than among non-Indigenous Australians (p<0·0001).
  - Among Indigenous Australians, significantly higher SRR of HIV diagnoses among men in the period 2012–15 than in previous periods (SRR 1·53, 95% CI 1·28–1·83; p<0·0001), and significantly higher diagnosis among Indigenous women (4·92, 4·02–6·02; p<0·0001) for the entire study period than among non-Indigenous women.
  - Concurrently, a decrease in HIV diagnoses of 1% per annum (RR 0·99, 95% CI 0·98–0·99; p<0·0001) across the study period was seen among non-Indigenous people. Indigenous Australians were more likely to be diagnosed at an advanced stage of HIV infection than non-Indigenous Australians (20·8% *vs* 15·1%; p=0·0088).
- Interpretation Greater efforts required
- Funding None.

James Ward et al, HIV LANCET Volume 5,September 2018,p e506-514

Targeted combination prevention to support female sex workers in Zimbabwe accessing and adhering to antiretrovirals for treatment and prevention of HIV (SAPPH-IRe): a cluster-randomised trial

- Strengthening engagement of female sex workers with health services is needed to eliminate HIV. Assessed the efficacy of a targeted combination intervention for female sex workers in Zimbabwe.
- Methods
  - a cluster-randomised trial from 2014 to 2016.
  - Clusters were areas surrounding female sex worker clinics and were enrolled in matched pairs.
  - Sites were randomly assigned (1:1) to receive usual care
  - The primary outcome was the proportion of all female sex workers with HIV viral load 1000 copies per mL or greater, assessed through respondent driven sampling surveys.
  - They also adapted cluster-summary approach to estimate risk differences.

Frances Mcowan et al, LANCET HIV,Volume 5 August 2018 p e417-426

Targeted combination prevention to support female sex workers in Zimbabwe accessing and adhering to antiretrovirals for treatment and prevention of HIV (SAPPH-IRe): a cluster-randomised trial

- Findings
  - Randomly assigned 14 clusters to usual care or the intervention (seven in each group).
  - 3612 female sex workers attended clinics in the usual-care clusters and 4619 in the intervention clusters during the study.
  - Half as many were tested (1151 *vs* 2606) and diagnosed as being HIV positive (546 *vs* 1052) in the usual-care clusters.
  - The proportion of all female sex workers with viral loads of 1000 copies per mL or greater fell in both study groups (from 421 [30%] of 1363 to 279 [19%] of 1443 in the usual-care group and from 399 [30%] of 1303 to 240 [16%] of 1439 in the intervention group), but with a risk difference at the end of the assessment period of only –2·8% (95% CI –8·1 to 2·5, p=0·23).
  - Among HIV-positive women, the proportions with viral loads less than 1000 copies per mL were 590 (68%) of 869 in the usual-care group and 588 (72%) of 828 in the intervention group at the end of the assessment period, adjusted risk difference of 5·3% (95% CI –4·0 to 14·6, p=0·20). There were no adverse events.

Frances Mcowan et al, LANCET HIV,Volume 5 August 2018 p e417-426

Targeted combination prevention to support female sex workers in Zimbabwe accessing and adhering to antiretrovirals for treatment and prevention of HIV (SAPPH-IRe): a cluster-randomised trial

- Interpretation
  - Our intervention of a dedicated programme for female sex workers led to high levels of HIV diagnosis and treatment. Further research is needed to optimise programme content and intensity for the broader population.
- Funding UN Population Fund (through Zimbabwe's Integrated Support Fund funded by UK Department for International Development, Irish Aid, and Swedish International Development Cooperation Agency).

Frances Mcowan et al, LANCET HIV,Volume 5 August 2018 p e417-426

Subtype C ALVAC-HIV and bivalent subtype C gp120/MF59 HIV-1 vaccine in low-risk, HIV-uninfected, South African adults: a phase 1/2 trial

- Modest efficacy was reported for the HIV vaccine tested in the RV144 trial, which comprised a canarypox vector (ALVAC) and envelope (env) glycoprotein (gp120).
- These vaccine components were adapted to express HIV-1 antigens from strains circulating in South Africa, and the adjuvant was changed to increase immunogenicity.
- 12-month immunisation was added to improve durability.
- **Methods**
  - HVTN 100 is a phase 1/2, randomised controlled, double-blind trial at six community research sites in South Africa.
  - Randomly allocated adults (aged 18–40 years) without HIV infection and at low risk of HIV infection to either the vaccine regimen **(intramuscular injection of ALVAC-HIV vector [vCP2438] at 0, 1, 3, 6, and 12 months plus bivalent subtype C gp120 and MF59 adjuvant at 3, 6, and 12 months)** or placebo, in a 5:1 ratio.
- Primary outcomes included safety and immune responses associated with correlates of HIV risk in RV144, 2 weeks after vaccination at 6 months (month 6·5).
- Compared per-protocol participants (ie, those who completed the first four vaccinations and provided samples at month 6·5) from HVTN 100 with stored RV144 samples assayed contemporaneously.

Linda-Gail Bekker et al; HIV Lancet Issue: Volume 5, July 2018, p e366-378

Subtype C ALVAC-HIV and bivalent subtype C gp120/MF59 HIV-1 vaccine in low-risk, HIV-uninfected, South African adults: a phase 1/2 trial

Findings

- Feb 9, 2015 and May 26, 2015
- 222 participants were included in the per-protocol analysis (185 vaccine and 37 placebo).
- 185 (100%) vaccine recipients developed IgG binding antibodies to all three vaccine-matched gp120 antigens with significantly higher titres (3·6–8·8 fold; all p<0·0001) than the corresponding vaccine-matched responses of RV144.
- The CD4+ T-cell response to the ev protein in HVTN 100 was 56·4% compared with a response of 41·4% in RV144 (p=0·0050).
- The IgG response to the (V1V2) env antigen in HVTN 100 was 70·5% (95% CI 63·5–76·6; n=129 responders), lower than the response to V1V2 in RV144 (99·0%, 95% CI 96·4–99·7; n=199 responders).

Interpretation

- Although the IgG response to the HVTN 100 vaccine was lower than that reported in RV144, it exceeded the predicted 63% threshold needed for 50% vaccine efficacy using a V1V2 correlate of protection model.
- Thus, the subtype C HIV vaccine regimen qualified for phase 2b/3 efficacy testing, a critical next step of vaccine development.

Funding US NIAID and Bill & Melinda Gates Foundations

Linda-Gail Bekker et al; HIV Lancet Issue: Volume 5, July 2018, p e366-378

Microelimination could be a big deal for HCV and HIV services

- On October 10, the British HIV Association (BHIVA) announced ambitious targets for the elimination of hepatitis C virus (HCV) in patients with HIV by 2021.
- The aim is to cure HCV in 80% of those co-infected by April 2019, 90% by April 2020, and 100% by April 2021.
- Rapidly tackling HCV in a well defined population— in this case people with HIV—is known as microelimination.
- About 71 million people worldwide are infected with HCV, and around 2·3 million are co-infected with HCV and HIV.
- People with HIV are six times more likely to have HCV than are those without HIV.
- Co-infection can accelerate HCV disease and patients may develop more fibrosis, regardless of whether they receive effective treatment for HIV.
- If BHIVA's microelimination strategy is to be successful, testing and treatment services will need to target those vulnerable groups of patients who are frequently not reached.
- Microelimination strategies can help build momentum where logistic and political challenges hamper national plans for elimination. Microelimination could have a knock-on effect on new infections with fewer people able to transmit HCV.
- Formidable challenges lie ahead, but substantial opportunities exist for collaboration to achieve the target for HCV micorelimination in coinfected patients, particularly the hardest to reach populations who bear disproportionate burdens of both HIV and HCV.

Editorial, LANCET HIV, Volume 5 – Nov 2018

Guided internet-based intervention for people with HIV and depressive symptoms: a randomised controlled trial in the Netherlands

- Many people living with HIV have depressive symptoms, but some individuals do not receive adequate treatment.
- An online self-help intervention for people with HIV with depressive symptoms on the basis of previous research has been developed.
- The aim of this study was to investigate the effectiveness of the intervention on depressive symptoms in individuals with HIV.
- Methods
  - Randomised controlled trial
  - participants recruited from 23 HIV treatment centres in the Netherlands were eligible if they were aged 18 years and older, had been diagnosed with HIV at least 6 months before the study, and had mild to moderate depressive symptoms (Patient Health Questionnaire-9 [PHQ-9] score >4 and <20).
  - Individuals also had to speak English or Dutch and have internet access and an email address.
  - Participants were randomly assigned (1:1) to an internet-based intervention (Living positive with HIV) or an attention-only waiting-list control condition.
  - The primary outcome was depressive symptoms assessed with the PHQ-9 and the Center for Epidemiologic Studies Depression Scale (CES-D) at pretest, 8 weeks after baseline, and 3 months after completion of the intervention or control condition (post-test 2).
  - The primary analysis was done by intention to treat.

Sanne Van Luenen et al, HIV Lancet:Volume 5,September 2018,pg e488-497

Guided internet-based intervention for people with HIV and depressive symptoms: a randomised controlled trial in the Netherlands

- Findings
  - Between Feb 1, and Dec 31, 2015, randomly assigned 188 participants to the intervention group (n=97) or the control group (n=91).
  - Mean pretest PHQ-9 score was 11·74 (SD 2·49) in the intervention group and 11·11 (2·37) in the control group; at the post-test visits it was 6·73 (3·00) and 6·62 (3·03) in the intervention group and 8·60 (3·12) and 8·06 (3·17) in the control group.
  - Mean pretest CES-D score was 24·91 (5·93) in the intervention group and 22·94 (6·48) in the control group; at the post-test visits it was 13·94 (6·39) and 15·71 (6·39) in the intervention group and 19·09 (7·05) and 18·43 (7·05) in the control group.
  - The reduction in depressive symptoms was significantly larger in the intervention group than in the control group (*d*=–0·56 [95% CI –0·85 to –0·27] for PHQ-9 and –0·72 [–1·02 to –0·42] for CES-D at post-test 1; –0·46 [–0·75 to –0·17] for PHQ-9 and –0·47 [–0·76 to –0·18] for CES-D at post-test 2
- Interpretation
  - This guided internet-based intervention might be effective for the treatment of depressive symptoms.
  - Future research should focus on the effectiveness of online psychological interventions for people with HIV who have mental health problems in low-income and middle-income countries.
- Funding Aidsfonds.

Sanne Van Luenen et al, HIV Lancet:Volume 5,September 2018,pg e488-497

Efficacy and safety of switching to fixed-dose bictegravir,emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1: 48 week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial

- Switching from boosted PI regimen to bictegravir, emtricitabine, and TAF could have many advantages.
- Report of 48 week results of a phase 3 study investigating this switch.
- Method
  - Multicentre, randomised, controlled, open-label, non-inferiority, phase 3 trial.
  - 121 outpatient centres in ten countries.
  - >18 years, eGFR of 50 mL/min or higher, had been virologically suppressed (<50 copies/ml) for 6 months or more, and were on a regimen consisting of boosted atazanavir or darunavir plus either emtricitabine and TDF or abacavir and lamivudine.
  - Computer-generated randomisation(1: 1) sequence, to switch to co-formulated once-daily bictegravir (50 mg), emtricitabine (200 mg), and TAF(25 mg), (bictegravir group) or to remain on their baseline boosted PI regimen , for 48 weeks.
  - The primary endpoint was the proportion of participants with plasma HIV-1 RNA of 50 copies/ mL or higher at week 48.
  - Efficacy and safety analyses included all participants who received at least one dose of study drug.

Eric S Dar et al; HIV Lancet Issue: Volume 5, July 2018, p e347- e355

Efficacy and safety of switching to fixed-dose bictegravir,emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressedadults with HIV-1: 48 week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial

- Results : Dec 2, 2015, and July 15, 2016,
  - Total- 577 (290 -- bictegravir group ; 287 -- boosted PI group).
  - At week 48, 5 participants (2%) in the bictegravir group and 5 (2%) in the boosted PI group had plasma HIV-1 RNA of 50 copies/mL or higher (difference 0·0%, 95·002% CI −2·5 to 2·5), thus switching to the bictegravir regimen was non-inferior to continued boosted PI therapy.
  - The overall incidence and severity of adverse events was similar between groups, although headache occurred more frequently in the bictegravir group than in the boosted PI group.
  - 80% of participants in the bictegravir group and 79% in the boosted protease inhibitor group had an adverse event.
  - 2 (1%) participants in the bictegravir group and 1 (<1%) in the boosted PI group discontinued treatment because of adverse events.
  - 54 participants (19%) in the bictegravir group had drug-related adverse events compared with six (2%) in the PI group.
- Interpretation : Non inferior.
- Funding Gilead Sciences.

Eric S Dar et al; HIV Lancet Issue: Volume 5, July 2018, p e347- e355

Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial

- Bictegravir, co-formulated with emtricitabine and TAF , has shown good efficacy and tolerability.
- 48-week results of a phase 3 study investigating switching to bictegravir, emtricitabine, and TAF from dolutegravir, abacavir, and lamivudine in virologically suppressed adults with HIV-1 infection.
- Methods
  - Multicentre, randomised, double-blind, active-controlled, non-inferiority, phase 3 trial, HIV-1-infected adults were enrolled at 96 outpatient centres in nine countries.
  - Age- 18 years or older and on a regimen of 50 mg dolutegravir, 600 mg abacavir, and 300 mg lamivudine (fixed-dose combination or multi-tablet regimen); eGFR of 50 mL/min or higher; and had been virologically suppressed (plasma HIV-1 RNA <50 copies per mL) for 3 months or more before screening.
  - Computer-generated randomisation (1:1) sequence, to switch to co-formulated bictegravir, emtricitabine and TAF , or to remain on dolutegravir, abacavir and lamivudine once daily for 48 weeks.
- The investigators, participants, study staff, and individuals assessing outcomes were masked to treatment assignment.

Jean-Michel Moline et al, HIV LANCET Issue: Volume 5,July 2018, pg e357-365

Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial

- The primary endpoint was the proportion of participants with plasma HIV-1 RNA of 50 copies per mL or higher at week 48 ; the pre-specified non-inferiority margin was 4%.
- The primary efficacy and safety analyses included all participants who received at least one dose of study drug.
- Between Nov 11, 2015, and July 6, 2016, 567 participants were randomly assigned and 563 were treated (282 received bictegravir, emtricitabine, and TAF , and 281 received dolutegravir, abacavir, and lamivudine).
- Switching to the bictegravir regimen was non-inferior to remaining on dolutegravir, abacavir, and lamivudine for the primary outcome: three (1%) of 282 in the bictegravir group had HIV-1 RNA of 50 copies per mL or higher at week 48 versus one (<1%) of 281 participants in the dolutegravir group (difference 0·7%, 95·002% CI −1·0 to 2·8; p=0·62).
- Treatment-related adverse events were recorded in 23 (8%) participants in the bictegravir group and 44 (16%) in the dolutegravir group.
- Treatment was discontinued because of adverse events in six (2%) participants in the bictegravir group and in two (1%) participants in the dolutegravir group.

Jean-Michel Moline et al, HIV LANCET Issue: Volume 5,July 2018, pg e357-365

Potential effectiveness of long-acting injectable pre-exposure prophylaxis for HIV prevention in men who have sex with men: a modelling study

Brandon D L Marshall et al, LANCET HIV: Volume 5,September 2018, pg e498-505

Potential effectiveness of long-acting injectable pre-exposure prophylaxis for HIV prevention in men who have sex with men: a modelling study

Introduction

- Long-acting injectable cabotegravir (GSK1265744) an integrase inhibitor formulated as an injectable nanoparticle suspension, exerts a strong protective effect against intravenous SIV challenge in a macaque model.
- Safety and tolerability of long-acting cabotegravir injections in HIV-uninfected men have been demonstrated in two phase 2a trials.
- In these trials, cabotegravir injections were well tolerated, with an acceptable safety profile despite high incidence of transient, mild-to-moderate injection-site reactions

Potential effectiveness of long-acting injectable pre-exposure prophylaxis for HIV prevention in men who have sex with men: a modelling study

- Pharmacokinetic data have suggested that long-acting injectable cabotegravir might confer consistent high levels of protection when given every 8 weeks.
- The efficacy of this regimen is being compared with oral PrEP in MSM at high risk of HIV infection at ten sites in eight countries as part of a phase 3 trial (NCT02720094).
- Although long-acting injectable PrEP is a promising HIV prevention approach, the population-level impact on the incidence of HIV infection in MSM is unknown.
- An agent-based model was used to quantify the potential effect of long-acting injectable PrEP on HIV incidence in a population of MSM in Atlanta, GA, USA, an area with high HIV incidence in MSM.
- The primary objective of this PrEP on cumulative HIV incidence in MSM in Atlanta over10 years, compared with the use of daily oral PrEP.

Potential effectiveness of long-acting injectable pre-exposure prophylaxis for HIV prevention in men who have sex with men: a modelling study

Model setting

- The agent-based model simulated HIV transmission over 10 years beginning in 2015 within a population of MSM (aged 18–64 years) in the city of Atlanta,GA, USA.
- Demographic, behavioural, and clinical characteristics, including race (ie, black/African-American or white), were assigned to each agent in the model, with distributions for these characteristics informed by local data and existing literature.
- The agent-based model simulated a dynamic population in steady state, in which agents left the population at death or due to ageing out at 65 years.
- The model was calibrated to reproduce the trajectories in observed HIV diagnoses in MSM in Georgia, USA, from 2007 to 2015.

Potential effectiveness of long-acting injectable pre-exposure prophylaxis for HIV prevention in men who have sex with men: a modelling study

	Description
Demographics	
Population size	n=11 245
Age	General male population distribution (age 18–64 years)
Mortality	Varies by HIV/AIDS status
HIV risk behaviours	
Per-partner sex frequency	Number of sex acts per partner per year
Per-act probability of condomless anal intercourse	Varies by number of previous contacts with partner
Per-act transmission risk (condomless anal intercourse)	Varies by sexual role, PrEP, HIV diagnosis, ART Receptive partner base risk: 1·38% per act Insertive partner base risk: 0·11% per act
Sexual networks	
Partner number (annual)	Number of anal sex partners per year
Duration of relationships	Duration of relationship in months
Daily oral PrEP	
Population-level coverage	Percentage of agents using daily oral PrEP
Probability of retention in clinical care	3 months after initiation: 72·5% 6 months after initiation: 59·6%
Probability of full adherence (≥4 pills per week)	92·3%
Percentage reduction in per-act transmission risk	96·0% (≥4 pills), 76·0% (2–3 pills)
Long-acting injectable PrEP	
Population-level coverage	Percentage of agents using long-acting injectable PrEP
Probability of retention in clinical care	2 months after initiation: 84·8%
Percentage reduction in per-act transmission risk	Varies as a function of time since last injection
HIV testing	
Probability of having ever tested	92·8%
Annual probability of obtaining HIV testing	69·0%
HIV treatment	
Proportion of PLWH aware of their HIV infection status	84·4% (white MSM), 74·7% (black MSM)
Proportion of PLWH on ART	46·7% (white MSM), 26·2% (black MSM)
Proportion of PLWH with viral load suppression	40·5% (white MSM), 21·0% (black MSM)
Percentage reduction in per-act transmission with ART	96·0% in PLWH with viral load suppression

A full list of parameter values, sources, and discussion are provided in the appendix. PrEP=pre-exposure prophylaxis. ART=antiretroviral therapy. PLWH=people living with HIV. MSM=men who have sex with men.

Table: Key model processes and parameters

Potential effectiveness of long-acting injectable pre-exposure prophylaxis for HIV prevention in men who have sex with men: a modelling study

Network structure

- As the model progressed in monthly time-steps over a period of 10 years, agents formed and dissolved sexual partners, engaged in sexual acts, and acquired HIV infection within serodiscordant partnerships.
- Target annual partner numbers and numbers of sex acts per partner were assigned to agents in a random fashion each year.
- Upon formation, each partnership was assigned a set duration.
- Population sexual networks were generated within the model through the formation and dissolution of relationships as the model progressed.

Potential effectiveness of long-acting injectable pre-exposure prophylaxis for HIV prevention in men who have sex with men: a modelling study

Estimated efficacy of long-acting injectable PrEP

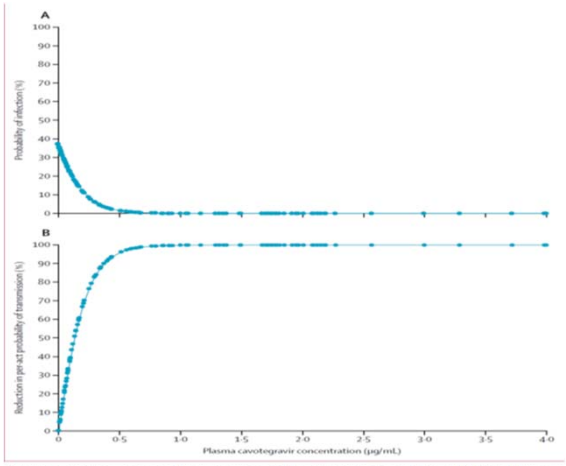

Figure 1: Estimated probability of infection from rectal SIV exposure in a macaque model (A),[11] and reduction in per-act probability of SIV transmission in macaques (B), by plasma cabotegravir concentration
SIV=simian immunodeficiency virus.

Potential effectiveness of long-acting injectable pre-exposure prophylaxis for HIV prevention in men who have sex with men: a modelling study

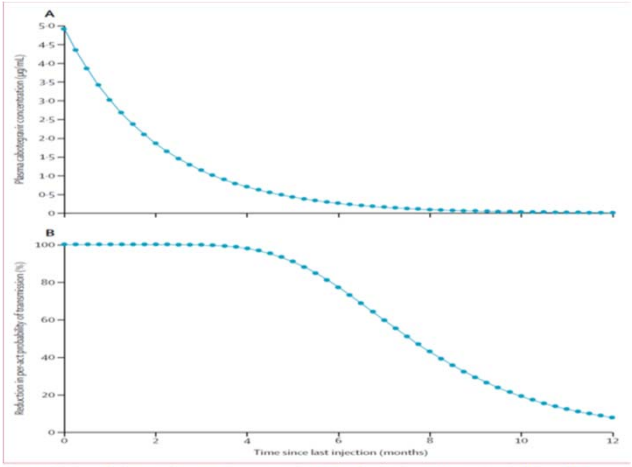

Figure 2: **Estimated plasma cabotegravir concentration (A) and reduction in per-act probability of HIV transmission (B), by time since last injection**
Percentage reduction in per-act HIV transmission after a final long-acting cabotegravir injection was estimated on the basis of half-life values reported by Markowitz and colleagues.[17]

Potential effectiveness of long-acting injectable pre-exposure prophylaxis for HIV prevention in men who have sex with men: a modelling study

Model scenarios

- The main analyses assessed three scenarios: oral PrEP exclusively; long-acting injectable PrEP exclusively; and no PrEP availability.
- 10 year cumulative HIV incidence was calculated for each of these three scenarios across coverage targets ranging from 5% to 35% in 5% increments.
- Each scenario was initialised in January, 2015, with a set coverage level of each intervention that was maintained throughout the 10 year simulation.
- In all cases, agents who were not retained in PrEP care were eligible to restart daily oral PrEP or long-acting injectable PrEP 12 months after discontinuation, with the same probability as all other HIV-uninfected agents.

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- For scenarios involving daily oral PrEP, agents, engagement in care was based on data regarding adherence and retention from MSM in three real-world PrEP clinics in the USA .
- Parameters pertaining to PrEP use were based on the assumption that a patient will receive a 90 day prescription at each clinical care visit and that a patient is considered retained in care if he had a clinical care visit in the past 6 months.
- Patients were categorised as not retained in care (and therefore no longer users of PrEP) if they had not had a clinical care visit within 6 months.
- This definition of retention in care does not allow for intermittent clinic attendance but does allow for variation in the length of time an individual uses PrEP.
- Active oral PrEP users were also categorised as optimally adherent or suboptimally adherent to capture heterogeneity in daily pill-taking.

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- For scenarios involving long-acting injectable PrEP, agents' engagement in care was based on observed retention rates in phase 2 trials of cabotegravir as long-acting injectable PrEP.
- In these cases, a patient was considered retained if they returned for a follow-up injection, occurring 2 months after their previous injection.
- For long-acting injectable PrEP, retention in care and adherence are interchangeable, because of the need for an individual to attend a clinic visit and for a clinician to administer the injections.

Potential effectiveness of long-acting injectable pre-exposure prophylaxis for HIV prevention in men who have sex with men: a modelling study

- **Outcomes**
  - The primary outcome was the cumulative number of new HIV infections over 10 years (2015–24) with either oral PrEP or long-acting injectable PrEP at each coverage level compared with the base model in which neither method was available.
  - Outcomes were also expressed as a percentage reduction in the cumulative number of new HIV infections.
  - Additionally, the percentage reduction in the cumulative number of new HIV infections in scenarios with long-acting injectable PrEP from scenarios with oral PrEP at the same coverage level is presented as a measure of the performance of long-acting injectable PrEP.
  - All scenarios were run 500 times.
  - Estimates are presented with 95% simulation intervals (SIs) to represent the overall stochasticity of the model.

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- **Funding**
  - National Institute on Drug Abuse and National Institute of Mental Health
  - Funders had no role in the study design

Potential effectiveness of long-acting injectable pre-exposure prophylaxis for HIV prevention in men who have sex with men: a modelling study

- **Results**
  - The agent-based model simulated a total of 11245 MSM in the city of Atlanta.
  - In a model without either of the two PrEP methods, there were an estimated 2374 new HIV infections (95% SI 2345–2412) from 2015 to 2024, producing an average 10 year incidence of 3·57 (3·42–3·70) per 100 person-years.
  - Estimated percentage reduction in infection per exposure as a function of plasma cabotegravir concentration yielded a theoretical efficacy for the 2 month period after an injection of more than 99·9% (this level of protection was assumed to be maintained as long as an individual is retained in care).
  - In the period after a final injection (ie, when a patient discontinues therapy), the level of protection diminished in accordance with the published half-life of long-acting cabotegravir

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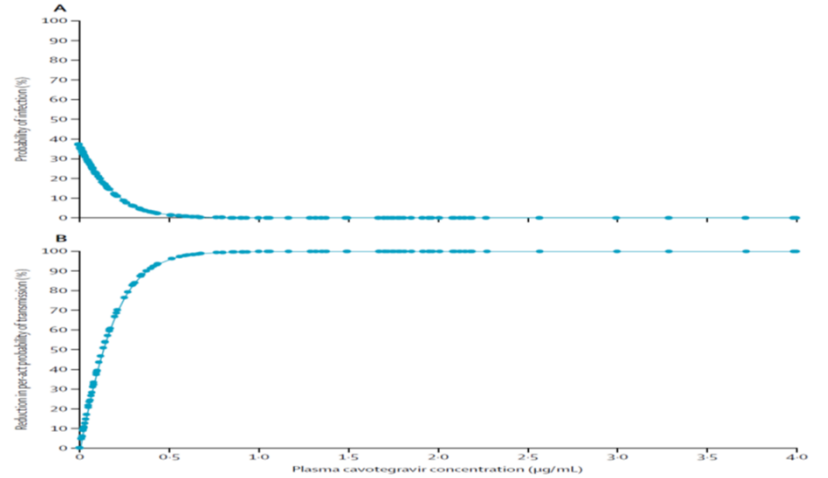

Figure 1: **Estimated probability of infection from rectal SIV exposure in a macaque model (A),[11] and reduction in per-act probability of SIV transmission in macaques (B), by plasma cabotegravir concentration**
SIV=simian immunodeficiency virus.

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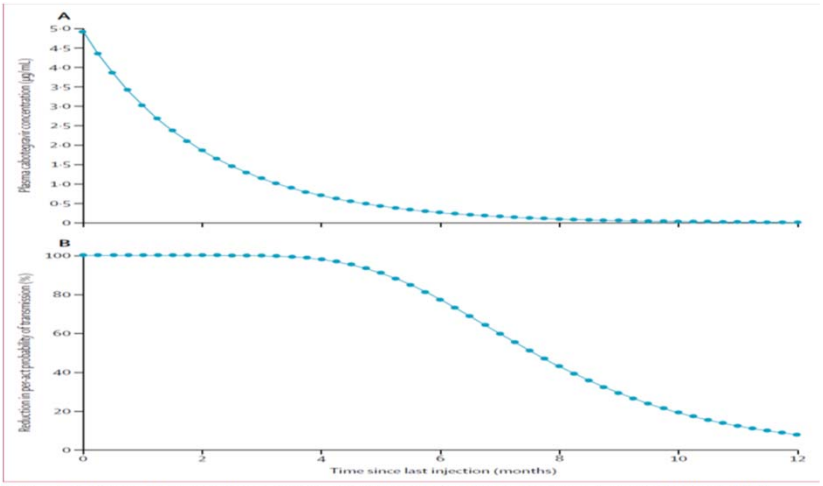

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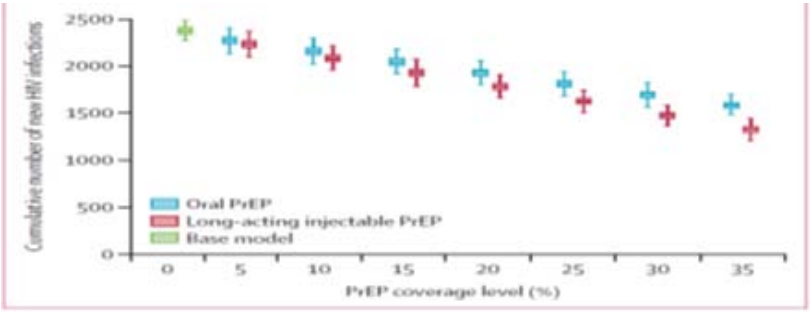

Figure 3: **Estimated cumulative number of new HIV infections in adult men who have sex with men in Atlanta (2015–24) at different coverage levels of daily oral PrEP, long-acting injectable PrEP, and a base case assuming no PrEP**
For each prevention method and coverage level, a box and whisker plot is shown, indicating the median cumulative number of new HIV infections, along with the first and third quartiles associated with this distribution. Whisker lengths represent the range of values larger than the third quartile plus 1·5 × IQR, and the range of values smaller than the first quartile minus 1·5 × IQR. Dots indicate outlying extreme values outside of this range. PrEP=pre-exposure prophylaxis.

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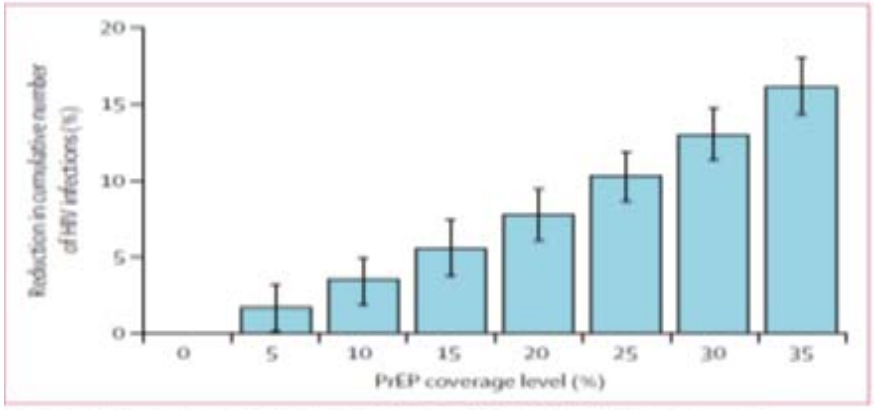

***Figure 4*: Percentage reduction in number of new HIV infections with long-acting injectable PrEP relative to daily oral PrEP**
The average percentage reduction is plotted comparing the number of new HIV infections with long-acting injectable PrEP relative to daily oral PrEP. Error bars show 95% simulation intervals. PrEP=pre-exposure prophylaxis.

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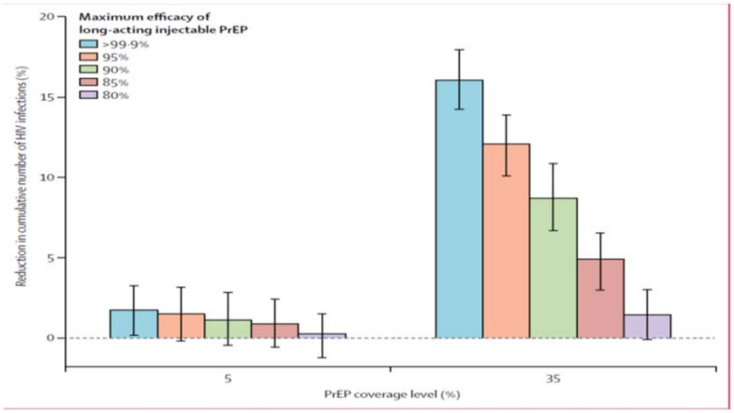

***Figure 5*: Percentage reduction in cumulative number of new HIV infections with long-acting injectable PrEP relative to equivalent coverage of daily oral PrEP, with varying maximum efficacy of long-acting injectable PrEP**
The average percentage reduction is plotted comparing the number of new HIV infections with long-acting injectable PrEP relative to daily oral PrEP. Error bars show 95% simulation intervals. PrEP=pre-exposure prophylaxis..

Potential effectiveness of long-acting injectable pre-exposure prophylaxis for HIV prevention in men who have sex with men: a modelling study

- Discussion
  - This study is the first to investigate the potential population-level effect of long-acting injectable PrEP on HIV incidence in MSM.
  - The model predicts that, with an estimated theoretical efficacy of greater than 99% protection from HIV acquisition with bimonthly cabotegravir injections and waning protection for up to12 months after a final injection, long-acting injectable PrEP prevents more HIV infections than daily oral PrEP at the same coverage level.
  - Should its efficacy in people be equivalent to its efficacy in reducing risk of SIV infection in macaques, long-acting injectable PrEP will be a highly promising HIV prevention approach.

Potential effectiveness of long-acting injectable pre-exposure prophylaxis for HIV prevention in men who have sex with men: a modelling study

- Two studies have investigated the effect of long-acting injectable PrEP on HIV incidence in heterosexual couples in South Africa.
- Walensky and colleagues24 used a state-transition model to compare scenarios in which daily oral PrEP was 62% effective and long-acting injectable PrEP was 75% effective versus a scenario in which no PrEP methods were available.
  - The lifetime risk of HIV infection
    - declined from 630 cases per 1000 with no PrEP use
    - 540 cases per 1000 with daily oral PrEP
    - 510 cases per 1000 with long-acting injectable PrEP.
  - These estimates are consistent with the study finding that long-acting injectable PrEP outperformed daily oral PrEP at all levels of coverage in reducing HIV transmission in target population (ie, MSM).
- In a dynamic compartmental model representing heterosexual adults in KwaZulu-Natal, South Africa, Glaubius and colleagues25 found that 9·1% of new HIV infections were prevented over a 10 year period in a scenario in which long-acting injectable PrEP was used by 15% of all heterosexual adults.
  - The results from this model are broadly similar (the use of long-acting injectable PrEP by 15% of MSM prevented 19% of new infections compared with no PrEP).

Potential effectiveness of long-acting injectable pre-exposure prophylaxis for HIV prevention in men who have sex with men: a modelling study

- These two previous modelling studies used different, arbitrary estimates for the efficacy of long-acting injectable PrEP, ranging from 70% to 90%.
- This model, based on raw data from a macaque challenge study, included an estimate for efficacy of long-acting injectable PrEP of more than 99%.
- Notably, long-acting injectable PrEP did not substantially outperform oral PrEP when maximum efficacy of the bimonthly injection was reduced to 80%.
- Analysis incorporated a 12-month period of waning partial protection from HIV infection after a final injection that was based on the halflife reported in previous studies. however, there is variation in the length of the pharmacokinetic tail of cabotegravir in humans.

Potential effectiveness of long-acting injectable pre-exposure prophylaxis for HIV prevention in men who have sex with men: a modelling study

- In scenarios with a shorter half-life or without this waning period of protection, the number of new HIV infections averted by long-acting injectable PrEP also decreased.
- These two features of long-acting injectable PrEP (maximum efficacy and longevity of protection after a final injection) will be key features in determining its real-world impact.
- The efficacy and longevity of protection conferred by longacting PrEP injections are being investigated in phase 3 trials.
- A major concern in the implementation of long-acting injectable PrEP in clinical settings is that individuals who discontinue the injections would have subtherapeutic serum cabotegravir concentrations for up to 12 months, leading to the potential development of integrase inhibitor resistance.
- Real-world long-acting injectable PrEP programmes might not have a population-level impact if high discontinuation rates cannot be offset to some extent by efforts to attract new users or re-engage those who discontinue.
- Future studies should assess the effect of varying coverage and retention patterns on the effectiveness of long-acting injectable PrEP in MSM.

Potential effectiveness of long-acting injectable pre-exposure prophylaxis for HIV prevention in men who have sex with men: a modelling study

- **Critical review/ Limitations**
  - Clinical recommendations do not exist for long-acting injectable PrEP. Hence there could be under estimation of the possible effect of both prevention and method.
  - Models simulate scenarios in which they are exclusively taking the specific medication.
  - Assumed that the coverage and effectiveness of other interventions in the model (eg, HIV testing, access to treatment) remained stable over the course of the simulation.
  - several potentially important parameters were estimated using data from other localities or geographical scales, including annual distributions of numbers of sexual partners, sex acts, and frequency and concurrency of partnerships of longer duration, which can affect the overall impact of both strategies.

Potential effectiveness of long-acting injectable pre-exposure prophylaxis for HIV prevention in men who have sex with men: a modelling study

- **Conclusion**
  - In conclusion, on the basis of cabotegravir pharmacokinetic data from phase 2a trials and efficacy reported in macaque models, long-acting injectable PrEP is predicted to be more effective than daily oral PrEP for the prevention of HIV transmission in MSM.
  - However, the real-world population impact and relative benefits of long-acting injectable PrEP compared with oral PrEP will depend on its efficacy in humans, as assessed in ongoing phase 3 trials, as well as on discontinuation rates and the duration of protection conferred.


Thank
you!!