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EDITORIAL

This issue of HTB includes first reports from the recent HIV Treatment for Prevention (HIVR4P) and Glasgow conferences, both of which have comprehensive webcasts.

Glasgow reports include two presentations on neural tube defects and conception/pregnancy with integrase inhibitors - with no additional dolutegravir-associated cases.

Extended follow up results were presented on ibalizumab and fostemsavir, both of which provide options for multidrug resistant HIV, plus a study from Cameroon reporting dolutegravir to be non-inferior to low-dose efavirenz.

HIVR4P 2018 had an impressive diversity of studies that included looking at the very real difficulty of designing studies to show whether pipeline PrEP have activity. Multiple sessions covered new approaches to prevention including long-acting injections and broadly neutralising antibodies (bNABs).

An important talk in a session on U=U, emphasised that unlike sexual transmission, breastfeeding can still transmit HIV to the infant, even when the mother's viral load is undetectable on ART.

Further coverage from both meetings will be included in the December edition of HTB. Happy reading...

SUPPLEMENTS

U=U resources for UK clinics: free posters, postcards and factsheets

Please continue to order these free resources.

Subscriptions

To join the email list for HTB please register free online:

<http://i-base.info/htb/about/subscribe>

U=U
Undetectable = Untransmittable

Did you know that having an undetectable viral load on HIV treatment (ART) stops HIV transmission?

ART is not only good for your health - it also protects your partner.

U=U means that you don't need to use condoms if you were only using them to stop HIV transmission.

Leading UK doctors and researchers strongly support the U=U statement.

There's nothing to be afraid of! If you remain with sustained, undetectable levels of HIV in your blood, you cannot transmit HIV to your sexual partners.*

Professor Chris Dunn, Chair British HIV Association: UK guidelines state that HIV doctors should talk to all their patients about how ART stops transmission.

September 2018

What is U=U? U=U stands for: Undetectable = Untransmittable. It means that someone with an undetectable HIV viral load on ART cannot transmit HIV even without using condoms or PrEP.

What does U=U involve? The protection from ART depends on:
• Taking ART every day.
• Having undetectable viral load for at least 6 months.
• Continuing to take your meds every day.

How can U=U not be at risk? The only event is when HIV viral load is undetectable there is low risk virus in sexual fluids for an infection to occur.

U=U*
UNDETECTABLE viral load means HIV IS UNTRANSMITTABLE
www.i-base.info/u-equals-u

"A person with sustained undetectable levels of HIV in their blood cannot transmit HIV to their sexual partners."

* Undetectable = Untransmittable
Poster produced by HIV-Base and Research Centre (2018-2020)

i-Base 2018 appeal

Last year we launched a funding appeal to help i-Base continue to provide free publications and services.

Your help has been inspiring – and we hope this support will continue during 2018. If 1000 people support us with £5 a month we will be on course to meet our shortfall.

All help is appreciated.

<http://i-base.info/i-base-appeal-we-need-your-help>

CONFERENCE REPORTS

Glasgow HIV Congress (Glasgow 2018)

28 – 31 October 2018, Glasgow

Introduction

The biennial Glasgow HIV Congress was held this year from 28 – 31 October and included numerous oral presentation with more than 300 studies also presented as posters.

Abstracts are available online as a supplement to the Journal of the IAS. The document is available as a PDF file or a continuous html page.

<https://onlinelibrary.wiley.com/toc/17582652/2018/21/S8>

<https://onlinelibrary.wiley.com/doi/full/10.1002/jia2.25187>

Webcasts from the conference will be available on the main conference website, usually within a couple of weeks.

<http://hivglasgow.org>

The following reports are included in this issue of HTB.

- No additional new neural tube defects with preconception dolutegravir: reports from three birth outcome cohorts

- Insufficient data on risk of neural tube defects with exposure to elvitegravir or bictegravir exposure during preconception or first trimester
- Viral dynamics of dolutegravir-based dual versus triple ART
- Ibalizumab: 48-week phase 3 results in participants with MDR HIV
- Fostemsavir: 48-week phase 3 results from BRIGHT E study
- Dolutegravir non-inferior to low dose efavirenz in real life African study conducted in Cameroon

No additional new neural tube defects with preconception dolutegravir: reports from three birth outcome cohorts

Polly Clayden, HIV i-Base

Three posters presented at Glasgow HIV 2018 showed data from analyses of dolutegravir (DTG) use in pregnancy from Canada, Frankfurt and Eastern/Central Europe. [1,2,3]

Although none of these reports found further neural tube defects (NTDs), after the possible risk found in Botswana, [4] numbers are small, so at best these findings are faintly reassuring.

Canadian Perinatal HIV Surveillance Program

The Canadian Perinatal HIV Surveillance Program (CPHSP) found no NTDs among 80 infants exposed to DTG in the first trimester.

The CPHSP is an active surveillance system which collects information on HIV positive women's pregnancies. From 2007 to 2017, there were 2,591 infants born to women in the CPHSP, of which 2,423 had data available on congenital anomalies and ART in pregnancy.

There were three neural tube defects reported in this cohort: 2/1311 exposed to ART at conception (0.15%). None were among the 80 infants with first trimester DTG exposure, including 69 exposed at the time of conception. The rate of NTDs in infants who were unexposed to ART in the first trimester was 1/690 (0.14%).

But there was a 3-fold higher rate of congenital anomalies (10.7%) in 28 infants with first trimester elvitegravir exposure.

The Frankfurt HIV Cohort

All women of the Frankfurt HIV Cohort who became pregnant and delivered between January 2008 and June 2018 were included in this retrospective study.

There were 274 pregnancies resulting in 281 infants. Fifty-two women (19%) received an integrase inhibitor: 48 raltegravir (RAL) and only four DTG (three of the four were switched to RAL during pregnancy week 4, 15 and 18). There were no NTDs among infants exposed to DTG.

Eastern and Central European Network Group

The Eastern and Central European Network Group collected epidemiological data on DTG use from 20 countries. Six countries provided detailed information on DTG exposure in pregnancy: Czech Republic, Finland, Greece, Poland, Slovakia and Turkey. Follow-up was to 31 May 2018.

In this cohort, 28 women took DTG in pregnancy; 24 started before conception. Although the report introduced the topic in the background information, the results did not include NTDs – so it is probably safe to assume that the investigators found none.

References

1. Money D et al. An analysis of congenital anomalies in pregnant women living with HIV in Canada: no signal for neural tube defects in women exposed to dolutegravir. HIV Glasgow. 28–31 October 2018. Glasgow, UK. Poster abstract P001.
2. Weisman D et al. Use of integrase inhibitors in HIV-positive pregnant women: data from the Frankfurt HIV Cohort. HIV Glasgow. 28–31 October 2018. Glasgow, UK. Poster abstract P002.
3. Kowalska J et al. Exposure to dolutegravir in pregnant HIV-positive women in Central and Eastern Europe and neighbouring countries: data from the ECEE Network Group. HIV Glasgow. 28–31 October 2018. Glasgow, UK. Poster abstract P004.
4. Clayden P. Potential safety signal for dolutegravir from the time of conception. HTB. 21 May 2018. <http://i-base.info/htb/34133>

Insufficient data on risk of neural tube defects with exposure to elvitegravir or bictegravir exposure during preconception or first trimester

Polly Clayden, HIV i-Base

A review of the Gilead global safety database, found no evidence of increased risk of neural tube defects (NTDs) with elvitegravir (EVG)- and bictegravir (BIC)-exposed pregnancies.

But this conclusion was based on limited (and extremely limited) numbers with all the usual caveats when many cases originate from respective reports drawn from a

population in which the denominator is unknown.

Findings from this review, conducted by the company, were presented at Glasgow HIV 2018. All pregnancies reported for women exposed to EVG- and BIC-containing products from the beginning of clinical development to 31 May 2018 were retrieved from the database. These cases were from clinical trials, Antiretroviral Pregnancy Registry (APR), spontaneous post marketing reports and literature review.

There were 630 EVG-exposed pregnancies of which 155 were prospectively reported and included preconception or first trimester exposure. There were no prospectively reported NTD cases.

One retrospective NTD was reported: a 34-year-old woman in the US who received EVG/cobicistat (COBI)/emtricitabine (FTC)/tenofovir alafenamide (TAF) before conception and then switched to raltegravir (RAL) + FTC/tenofovir disoproxil fumarate (TDF) 48 days after her last menstrual period. Medications started before conception were folate and metronidazole. An ultrasound 19 weeks after her last period showed anencephaly. She had a medical abortion at 19 weeks.

On 10 October 2018 (after the data lock for this review), another retrospective NTD case from 2014 was reported: a French woman of unknown age started EVG/COBI/FTC/TDF two weeks after her last menstrual period. Myelomeningocele was reported at 14 weeks gestational age and she had a medical abortion two weeks later.

For BIC-containing products, 25 pregnancy cases were identified, of which 18 were prospectively reported and included preconception or first trimester exposure. There were no cases of NTD found with review of the limited data from BIC.

C O M M E N T

The study investigators concluded: “Viewed in the context of more than 600 EVG-exposed pregnancies these two cases cannot be distinguished from the background rate in the general population”.

Yet they also wrote: “A prevalence rate could not be derived from these data, as many cases originated from retrospective reports, drawn from a population in which the number of exposed pregnancies is unknown”.

And finally: “Currently, there is no evidence of an increased risk of EVG- or BIC-containing products during pregnancy”.

It is always encouraging to see originator companies present safety reviews of their products publicly (and not only for birth outcomes). But as the 600 EVG-exposed pregnancies had a lot of missing data, including timing of exposure, and there were only 25 BIC-exposed ones, a better conclusion might be that there is insufficient evidence to dismiss or confirm a potential risk of NTDs with EVG or BIC.

Reference

Farrow T et al. Cumulative safety review of elvitegravir and bictegravir use during pregnancy and risk of neural tube defects. HIV Glasgow. 28–31 October 2018. Glasgow, UK. Poster abstract P030.

Viral dynamics of dolutegravir-based dual versus triple ART

Simon Collins, HIV i-Base

Two oral abstracts at the HIV Glasgow 2018 conference included additional analyses of viral dynamics when starting or switching to dolutegravir/lamivudine dual therapy, presented by Babafemi Taiwo from Northwestern University, Chicago.

The first was a new analysis from the phase 3 ASPIRE study on levels of residual viraemia on effective ART but using an ultrasensitive viral load test with a cut off of 0.5 copies/mL. [1]

This main ASPIRE study reported that switching to dolutegravir/lamivudine was non-inferior compared to remaining on triple therapy, based on maintaining viral suppression <50 copies/mL at 24 weeks. [2]

The new analysis included samples from baseline, week 24 and week 48 timepoints for 82 participants who continued in the study (41 from each arm), with results for all three timepoints available for 73 participants.

Baseline characteristics included median CD4 count of 677 cells/mm³ and median time of 5.8 years on ART. Baseline ART was based on integrase inhibitors (40%), NNRTIs (30%) or PIs (29%). Mean viral load was similar at 4.9 vs. 5.3 copies/mL in the dual vs triple therapy groups.

After adjusted for small non-significant baseline levels, the differences in viral loads continued to be similar in both groups at week 24 (difference 1.3 copies/mL, 95%CI: -2.1 to +4.7, p = 0.45) and week 48 (difference 0.5 copies/mL, 95% CI: -2.9 to +3.9, p = 0.77).

There were also no differences when results were analysed by baseline CD4 count (above or below 500 cells/mm³) or previous duration of ART (using cut points of more vs less than six years).

The second study looked at the early viral dynamics of starting dolutegravir/lamivudine in treatment naive participants in the pilot AACTG5353 study compared to dolutegravir-based triple therapy in the SPRING-1 and SINGLE studies. [3]

Samples were available from weeks 0, 2, 4, 8, 12, 16 and 24 to look at 2- vs 3-drug ART and baseline viral load (< vs. > 100, 000 copies/mL).

Overall, there were no significant differences between 2- vs 3-drug groups ($p < 0.001$), but baseline viral load $>100,000$ copies/mL was associated with a slower rate of viral decay. Although not statistically significant, the viral decay rate was slightly steeper in the dual therapy study. See Table 1.

Table 1: Viral decay by baseline viral load

	2-drug	3-drug
$<100,000$ copies/mL	1.272	0.969
$>100,000$ copies/mL	0.725	0.596

C O M M E N T

These more detailed results from dual therapy studies show similar level of potency for dolutegravir/lamivudine compared to three-drug ART. There was also no evidence of low level viral rebound below the 50 copies/mL cut-off after switching from triple therapy ART.

The same group have recently published an analysis of HIV genital shedding in a sub-study of ASPIRE, reporting no differences between dual and triple dolutegravir-based ART. [4]

The fixed-dose formulation of dolutegravir/lamivudine has already been submitted to the EMA based on results from the GEMINI 1 and 2 studies. [5]

References

Unless stated otherwise, references are to the Abstract from the Glasgow HIV Congress 2018, 28 – 31 October 2018. Available free online. <https://onlinelibrary.wiley.com/toc/17582652/2018/21/S8>

1. Taiwo B et al. No significant changes to residual viremia after switch to dolutegravir and lamivudine in a randomized trial. Glasgow HIV Congress 2018, 28 – 31 October 2018. Oral abstract O213.
2. Taiwo B et al. Dolutegravir plus lamivudine maintain HIV-1 suppression through week 48 in a pilot randomized trial. Clin Infect Dis. 2017 Dec 26.
3. Gillman J et al. Comparable viral decay with dolutegravir plus lamivudine versus dolutegravir-based triple therapy. Glasgow HIV Congress 2018, 28 – 31 October 2018. Oral abstract O213.
4. Gianella S et al. Genital HIV-1 shedding with dolutegravir (DTG) plus lamivudine (3TC) dual therapy. JAIDS Journal of Acquired Immune Deficiency Syndromes Publish Ahead of Print DOI: 10.1097/QAI.0000000000001863.
https://journals.lww.com/jaids/Citation/publishahead/Genital_HIV_1_Shedding_with_Dolutegravir__DTG_.96543.aspx
5. Dolutegravir/lamivudine FDC submitted to EMA and FDA. HTB 19 October 2018.
<http://i-base.info/htb/35124>

Ibalizumab: 48-week phase 3 results in 27 participants with MDR HIV

Simon Collins, HIV i-Base

Ibalizumab is a monoclonal antibody that was recently approved in the US under an orphan drug status for treatment of multidrug resistant HIV.

The phase 3 results from the registrational TMB-301 study were recently published reporting with 43% of 40 treatment-experienced participants sustaining viral load <50 copies/mL at week 24 by ITT analysis (median 1.8 log drop) and 55% by completer analysis (median 2.5 log drop), using ibalizumab with optimised background therapy. [1]

Entry criteria included having multidrug resistance (to at least three classes) and on virologically failing ART. Baseline characteristics included median viral load of 36,000 copies/mL with 7/40 >100,000 copies/mL. Median CD4 count was 73 cells/mm³ with 2/40 <100 cells/mm³ and 13/40 <10 cells/mm³. Median duration of HIV infections was 23 years (range: 2 to 30). More than 90% of participants had major mutations to each of the NRTI, NNRTI and PI classes and more than 70% had drug resistance to integrase inhibitors.

An oral presentation at Glasgow 2018 included longer follow up for 27 participants out to 48-weeks in the open label expanded access extension (TBM-311). Although new participants joined the expanded access study, this presentation only included results from those who rolled over from the phase 3 TMB-301 study. From weeks 25-48, ibalizumab was continued at a 800 mg IV dose every two weeks, with optimised background therapy. [2]

The most important results – and the clearest new data from the presentation – was that 15/27 participants who had undetectable viral load at week 25, continued to maintain undetectable viral load to week 48. Three participants also discontinued early due to withdrawn consent or investigator decision – for reasons that were all judged not related to ibalizumab. No new safety concerns were reported with no drug-related discontinuations.

However, no individual details were presented on the remaining 9/27 participants who had detectable viral load at week 25, in terms of viral load, CD4 count or development of drug resistance.

Further details were presented in a poster for participants in the TMB-301 study that didn't achieve the early primary endpoints of >0.5 log copies/mL viral suppression at days 7, after the initial loading dose of ibalizumab (at 2000 mg) was added as monotherapy to the baseline failing ART. [3]

Overall, although mean viral load reduction was 1.1 log copies/mL, 7/40 participants (see baseline criteria outlined above) did not achieve >0.5 log copies/mL after a week of monotherapy.

Of these, 4/7 did report more significant viral suppression after the background regimen was optimised after the 7-day monotherapy. These were generally participants with lower baseline viral load and whose treatment optimisation included a switch to different drugs, including twice-daily dolutegravir. This makes it difficult to understand the contribution made by ibalizumab.

C O M M E N T

These results confirm that ibalizumab can contribute to long-term viral suppression if used as part of a combination with other active HIV drugs.

However, the lack of data overall, including baseline susceptibility to ibalizumab, is not helpful, including in the NEJM paper, especially given the extremely low numbers of people who are in this study.

The limited dataset overall, really warrants more detailed results to be clearly presented for all participants. Further follow-up analysis are planned for week-96.

Ibalizumab was filed with the EMA in August 2018 for a decision on EU approval. [4]

References

1. Emu B et al. Phase 3 study of ibalizumab for multidrug-resistant HIV-1. *N Engl J Med* 2018; 379:645-654
DOI: 10.1056/NEJMoa1711460/ (16 August 2018).
<https://www.nejm.org/doi/full/10.1056/NEJMoa1711460>
2. Cohen Z et al. Analysis of patients completing the ibalizumab phase 3 trial and expanded access program. Glasgow HIV Congress 2018, 28 – 31 October 2018. Late breaker oral abstract O345.
3. DeJesus E et al. Outcomes of patients not achieving primary endpoint from an ibalizumab phase 3 trial. Glasgow HIV Congress 2018, 28 – 31 October 2018. Poster abstract P064.
4. HTB. FDA approves ibalizumab in the US to treat multidrug HIV resistance. (06 March 2018).
<http://i-base.info/htb/33659>

Fostemsavir: 48-week phase 3 results from BRIGHT study

Simon Collins, HIV i-Base

Two oral presentations provided 48-week safety, efficacy and subgroup analysis from the investigational gp120 attachment inhibitor fostemsavir.

As the first drug in a new class, this compound is especially important for people with drug resistance to their current last combination.

Although the primary endpoint was viral suppression to <40 copies/mL at day 8 after fostemsavir has been added to current failing ART, participants have now reached 48-weeks for secondary efficacy and safety endpoints. Other investigational drugs were allowed during the optimisation phase. The data at Glasgow 2018 update the week-24 results presented last years at the EACS 2017 conference.

As previously reported, this was an advanced patient group with CD4 count at screening less than 200 cells/mm³ in 72% and 50 cells/mm³ in 41% of the group. Previous use of integrase inhibitors and protease inhibitors were reported for 80% and 96% respectively.

Baseline characteristics for the randomised group included median age 44 years (range 18 to 73) and approximately 30% were women. Median (range) CD4 and viral load were approximately 100 cells/mm³ (0 to 1160) and 4.7 log copies/mL (1.6 to 6.9), respectively. Approximately 10% had no fully active drugs in the optimised background regimen (OBR), with 40-50% having only 1 or 2 fully active drugs.

Baseline characteristics were similar for the open-label group, with the important exception that 80% had no active drugs in the OBR and 20% had only one active drug. In this group, >95% had integrase experience and 70% had used T-20. Of the 19 people with sensitivity to one drug, 13/19 used the investigational mAb ibalizumab.

By week 24, viral suppression was reported for 54% of participants, with 71% and 77% using <200 and <400 copies/mL cut-offs respectively.

By week 48, follow-up included 79% (215/272) randomised participants and 68% (69/99) open label participants. Reasons for withdrawal are shown in Table 1.

Table 1: Reasons for study withdrawals by week 48

	Randomised n=57/272	Open label n=32/99
AEs	9 (3%)	5 (5%)
Lack of efficacy	12 (4%)	6 (6%)
Non-adherence	11 (4%)	5 (5%)
Withdrawn consent	5 (2%)	1 (1%)
Lost to follow-up	7 (3%)	1 (1%)
No longer met study criteria	3 (1%)	2 (2%)
Death	8 (3%)	12 (12%)
Pregnancy	1 (<1%)	
Other	1 (<1%)	

At week 48, by snapshot analysis, 54% participants in the randomised study (146/272) and 38% (38/99) in the open label study had viral load <40 copies/mL. These were similar to rates at week 24.

Over time, rates were higher by observed analysis: 57% vs 62% <40 copies/mL, 79% vs 84% <200 copies/mL and 85% vs 86% using the <400 copies/mL thresholds - all weeks 24 (n=246) vs 48 (n=233) respectively.

Mean CD4 responses also steadily increased in both groups over 48 weeks by +139 cells/mm³ and +63 cells/mm³ in the randomised and open label groups respectively.

Serious adverse events were common in both arms, reflecting the advanced HIV stage, but were higher in the open label group: 31% vs 44%; grade 3/4: 26% vs 47%; and deaths 4% vs 14%.

The sub group analysis by baseline CD4 count showed significant CD4 increases even for those starting with CD4 counts <20 cells/mm³, although viral response rates were lower for this group (35%).

Table 2: Fostemsavir subgroup analysis by baseline CD4 count

BL CD4 cells/mm ³	HIV viral load <40 c/mL		n	Change in CD4 cells/mm ³
	n	n (%)		Mean change (SD)
20	72	25 (35%)	58	145.2 (109.33)
20–50	25	12 (48%)	20	149.0 (93.20)
50–100	39	22 (56%)	30	126.4 (103.62)
100–200	63	37 (59%)	57	123.1 (101.13)
≥200	73	50 (68%)	63	150.0 (195.88)

References

1. Aberg J et al. Week 48 safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in heavily treatment-experienced participants (BRIGHTE study) . Glasgow HIV Congress 2018, 28 – 31 October 2018. Oral abstract O344A.
2. Molina J-M et al. Phase III study of fostemsavir in heavily treatment-experienced HIV-1 infected participants: BRIGHTE Week 48 sub- group analysis in randomised cohort participants . Glasgow HIV Congress 2018, 28 – 31 October 2018. Oral abstract O344B.

Dolutegravir non-inferior to low dose efavirenz in real-life African study conducted in Cameroon

Polly Clayden, HIV i-Base

Dolutegravir-based first-line ART was non-inferior, but not superior, to that with efavirenz 400 mg at week 48 in the NAMSAL study – according to findings presented at Glasgow 2018. [1]

Overall, approximately 70% of participants achieved viral load suppression to <50 copies/mL. But people with high viral load at baseline (>500,000 copies/mL) had poor virological response with less than 60% achieving <50 copies/mL in both arms.

NAMSAL ANRS 12313 is a phase 3 study designed to assess the safety and efficacy of a dolutegravir (DTG)- versus an efavirenz 400 mg (EFV-400)-based first-line regimen in a low-income country. Cameroon, is known for high HIV-1 genetic diversity, and has an increasing rate of NRTI- and NNRTI-transmitted resistance.

It is a randomised, open label, multicentre trial conducted at three sites in Yaoundé. HIV positive, ART-naive adults with viral load >1000 copies/mL were randomly assigned (1:1) to DTG or EFV-400, both with tenofovir disoproxil fumarate (TDF)/lamivudine (3TC).

The primary endpoint was the proportion of participants with viral load <50 copies/mL at week 48 (FDA ITT snapshot algorithm, 10% non-inferiority margin). A superiority test was planned if non-inferiority was demonstrated.

A total of 820 participants were screened: 204 were ineligible and 616 were randomised. Of these, 613 received at least one dose of study medication: 310 and 303 participants in the DTG and EFV-400 arms respectively.

Baseline characteristics were similar across both arms: 68% of participants were women, median age was 36 years (IQR: 29 to 43), CD4 count was 281 cells/mm³ (IQR: 154 to 444), and viral load was 5.3 log copies/mL (IQR: 4.8 to 5.8). A considerable proportion of participants had high viral load at baseline: 66% had >100,000 copies/mL and 30% had >500,000 copies/mL.

At week 48, the proportion of participants with viral load <50 copies/mL was 74.5% in the DTG arm and 69.0% in the EFV-400 arm: difference +5.5% (95% CI -1.6 to +12.7); p=0.13 for the superiority test.

Among participants with baseline viral load <100,000 copies/mL, the respective proportions were 91.3% and 83.5%: difference +7.8% (95% CI -1.2 to +16.8).

And for participants with >100,000 copies/mL at baseline, the respective proportions were 66.2% and 61.5%: difference +4.7% (95% CI -4.6 to +14.0).

Of participants with >500,000 copies/mL at baseline only 54.8% and 57.9% in the

DTG and EFV-400 arms respectively, achieved viral load <50 copies/mL at 48 weeks.

In ITT analysis for viral load <200 copies/mL the proportion were 89% for the DTG arm and 83.5% for the EFA-400 arm; and for <1000 copies/mL the respective proportions were 91.9% and 86.5%.

In multivariate analysis, viral load >100,000 copies ($p<0.0001$), CD4 count <200 cells/mm³ ($p=0.024$) and male sex ($p=0.017$) were associated with viral load >50 copies/mL at week 48.

Among 19 participants with virological failure >1000 copies/mL and genotype results: 0/3 in the DTG arm had resistance at baseline or at virological failure and 6/16 in the EFV-400 arm had baseline resistance and 3/16 participants who were susceptible at baseline had resistance at virological failure.

Overall 9% of participants had AIDS-defining events and there were no discontinuations of study medication due to intolerance.

C O M M E N T

NAMSAL results have been eagerly awaited as this is the first study to look at DTG in a real-life African setting. Unlike registrational studies, participants reflect the population that will be treated in a low-income country, including those with high baseline viral load who were less likely to achieve fully suppressed viral load.

Among participants presenting with high viral load at baseline, the investigators observed persistently low viral replication rates in both arms. The discussion following the presentation mainly focused on explanations for this, particularly in the DTG arm.

Principal investigator Eric Delaporte of the University of Montpellier noted that adherence was good in the study – greater than 80% in both arms.

Anton Pozniak of the Chelsea and Westminster Hospital, London explained that viral suppression with an integrase inhibitor usually occurs by about week 16 to 24 and asked if it was likely that it could take longer with very high viral loads and this is just the first time we have seen data from a large number of people in this group. Dr Delaporte remarked that this is “not an exceptional figure” in west and other parts of Africa and that there are a lot of further analyses to do.

NAMSAL will continue until 2021 to ensure long-term monitoring of participants who started DTG – hoping to confirm the absence of resistance mutations to this drug. [2]

References

1. Cournil A et al. Dolutegravir- versus an efavirenz 400 mg-based regimen for the initial treatment of HIV-infected patients in Cameroon: 48-week efficacy results of the NAMSAL ANRS 12313 trial. HIV

Glasgow. 28–31 October 2018. Glasgow, UK. Oral abstract O342.

2. ANRS/Unitaid press release. Dolutegravir, an alternative first-line HIV treatment for low and middle-income countries. 31 October 2018.

<https://unitaid.org/news-blog/dolutegravir-an-alternative-first-line-hiv-treatment-for-low-and-middle-income-countries/#en>

CONFERENCE REPORTS

3rd HIV Research for Prevention Conference (R4P2018)

21–25 October 2018, Madrid

Introduction

The Research for Prevention (R4P) conferences are held every two years to focus on vaccines, PrEP, microbicides, treatment as prevention and other biomedical prevention approaches.

This year the meeting was held in Madrid and attended by 1400 delegates.

The programme balanced a strong emphasis on basic science (vaccine-related studies, mAbs, pipeline PrEP) with a similar emphasis on practical issues of prevention research (who are accessing PrEP, including in different populations and including when people decide to start and stop).

With 138 oral abstracts and >600 posters, there were numerous other topics in between – although fewer clinical efficacy studies than previous years.

Comprehensive webcasts of the presentations from both plenary lectures and oral abstract sessions are now online, with a searchable abstract database and poster available in PDF format. Satellite sessions are also webcast.

Conference planner - with links to abstracts.

www.professionalabstracts.com/hivr4p2018/iplanner/#/grid

Webcasts.

<http://webcasts.hivr4p.org>

Programme highlights this year include the following themes.

- PrEP in practice: who is using PrEP, where and how - and who is still left out (many

given only 300,000 are estimated to access PrEP globally).

- Broadly neutralising antibodies (bNAbs) for both treatment and prevention (from newborns to adults).
- Pipeline PrEP, including both new drugs and new formulations (pills, injections, implants, rings etc).
- Pharmacokinetic, modelling and imaging studies showing delivery and distribution of PrEP drugs and including review of TDF/FTC levels in trans women.
- Treatment as prevention and U=U integration into clinical practice.

Reports included in this issue of HTB.

- How to evaluate PrEP and vaccines: urgency for next generation compounds
- Dual bNAb treatment maintains viral suppression for median 21 weeks off-ART
- Cabotegravir levels can be detected several years: PK tail to be covered by oral PrEP
- 3D imaging videos shows HIV infection might establish within hours
- bNAbs for HIV prevention: extended-release VRC01 and update on AMP prevention studies
- Why U=U does not cover breastfeeding

How to evaluate PrEP and vaccines: urgency for next generation compounds

Simon Collins, HIV i-Base

Several presentations at R4P2018 looked at the new challenges of evaluating efficacy of new PrEP and vaccine candidates.

They highlighted the urgency for new trial designs, using new endpoints and statistical approaches, given the ethical need for control arms to include oral PrEP as a standard of care. By definition, this reduces the number of people likely to become HIV positive compared to earlier placebo controlled studies.

Current studies for second generation PrEP either use an active control of oral TDF/FTC (for example, for long-acting cabotegravir injections and for F/TAF), or allow oral PrEP as a choice (as with the monoclonal antibody VRC01 AMP studies, at least in countries where oral PrEP is approved).

However, when these studies use hard endpoints of HIV infections as the primary endpoint, the non-inferiority against TDF/FTC or superiority over placebo becomes difficult to prove if very few people become HIV positive.

Instead, this low HIV incidence – which might easily drop further during the course of a study – makes traditional study designs unpractical as they would need to enrol much larger numbers of participants or follow them for many more years.

Defining need and new approaches

These issues were reviewed by Professor Sheena McCormack from the UK Medical Research Centre (MRC) in one of the plenary talks at the opening of the R4P2018 conference. [1]

The context for these discussions also include the different levels of evidence required by health commissioners and policy makers, even once clinical efficacy is proven and included in clinical guidelines. While first generation oral PrEP with TDF/FTC is approved by regulatory agencies such as the FDA and the EMA and is clearly effective, safe and cost effective, access remains extremely limited.

While background levels of HIV incidence should fall due to combination prevention including increased HIV testing, linkage to care with universal access to early ART, treatment as prevention, oral PrEP and voluntary medical male circumcision in some settings, HIV eradication on a population level still aims for an effective HIV vaccine as a key long-term goal. Yet the efficacy of current PrEP arguably sets a higher threshold for vaccine efficacy to likely >50% - just as ART raises the safety threshold for how good and how safe a cure has to be.

One new approach is to use a multi-arm multi-stage (MAMS) study design, and this is already being used for two European funded vaccine studies: the European HIV Vaccine Alliance (EVHA) and PrEPVacc.

The EVHA study testing three therapeutic interventions – two vaccines and a monoclonal antibody – uses an initially low stats barrier based on interim lack of benefit to progress to the second stage with a higher barrier to progress. [3]

The PrEPVacc study is comparing a dual preventative vaccine arm and a triple vaccine arm each to a shared control arm. PrEP will be given for the first six months while immune responses build, and there will be a comparison between TDF/FTC and TAF/FTC during this short-term use of oral PrEP. Again, an interim lack of benefit assessment is used for the first stage in order to progress the vaccine to the next stage with generous stats, but based on a 70% threshold for overall efficacy. [4]

Both studies are designed to fit the current maximum five-year funding criteria but longer studies using MAMS have the potential to be more efficient at finding effective interventions in shorter times. For example, the still-ongoing STAMPEDE study for prostate cancer originally randomised participants to one of five active arms with a

shared standard of care control arm in 2005. In this platform design, less effective intervention arms were steadily dropped and new interventions added. These new study arms were easy to rapidly enrol, and STAMPEDE now reports new efficacy results every 12-18 months that are powered to change standards of care. This design reduces the number of participants using less effective interventions and is flexible to changing standards of care.

Several years ago, an analysis using a similar approach modelled that some earlier HIV vaccine efficacy studies could have reached results in half the study time. [5]

Statistical interpretation of increasingly effective PrEP paradoxically can produce datasets with wider confidence intervals for the more effective intervention in similar size studies because there are so few events in both groups. One way to overcome these results is to incorporate a projected placebo rate using an inverted infection ratio (AIR). See Table 1.

Table 1: Studies with fewer events generate wider confidence intervals

	Incidence rate /100 years		IRR (90%CI)	AIR (90%CI)
	SoC TDF/ FTC r (n)	New PrEP r (n)		
Study A	2 (40)	2 (40)	1.00 (0.69,1.44)	1.00 (0.78,1.28)
Study B	1 (20)	1 (20)	1.00 (0.59,1.68)	1.00 (0.88, 1.14)

Based on 2000 PY observation in each arm

Surrogate markers for HIV infection

A second approach to overcome these challenges for PrEP studies was proposed by Jeff Murray from the US FDA who also emphasised that non-inferiority study designs using oral PrEP as an active control are not possible for women because of the lack of a consistently positive treatment effect in earlier PrEP studies. [6]

Even though non-inferiority study designs can theoretically still be used in gay men, the low expected infection rate would likely either significantly increase study size (>20,000 participants) or significantly extend follow-up time (>7- years). Either change would make phase 3 studies prohibitively expensive for even the most promising compounds to be studied.

Instead, PrEP studies could perhaps prove efficacy by showing a lack of expected events in a well-defined population in the absence of the intervention. A similar approach has been used to evaluate new oral contraceptives in single arm or active control arm studies using the Pearl index which is calculated based on consistency

of pregnancy in population level. Products typically have to show less than two unintended pregnancies per 100 patient years of follow-up, with the EMA requiring a sufficient sample size for the 95%CI for the Pearl Index to not be >1.0.

Even though HIV incidence without an intervention is lower than pregnancy, a similar index for HIV would involve a reliable estimate of expected HIV incidence in populations with significant risk and high prevalence.

For example, rates of indicator infections that correlate closely to likely HIV risk could use rate of rectal STIs. For this to be reliable requires the study population to be at risk for HIV relying on HIV prevalence and behaviour risk.

The close correlation between rectal gonorrhoeae (GC) and HIV incidence in gay men was shown from a systematic literature search that identified nine recent studies in gay men that collected incidence data on HIV and rectal GC. These results were used to generate an expected HIV incidence with appropriate 95%CIs for gay men based on background prevalence of GC.

New PrEP interventions for gay men could then use active control arms using current standard of care PrEP and measure efficacy based on rectal GC and other STI endpoints, in population where these rates are already high at baseline. The approach is dependent on defining an acceptable level of background HIV risk (also supported by prevalence at screening) and an assumption that behavioural change is unlikely.

Further discussions

A third presentation by Deborah Donnell from the Fred Hutchinson Cancer Research Center used examples of current PrEP studies to further expand on new approaches that will be essential now that current approaches to study design are inappropriate or infeasible in most settings. [7]

Studies comparing the new agent to active controls (F/TAF and cabotegravir trials) require all participants to agree to use something. Layer study designs (for VRC01 AMP studies or HVTN vaccine studies) use placebo but allow everyone to use of oral TDF/FTC. In populations with a background HIV incidence of 1%, and similar efficacy in both arms, this would require studies involving 40,000 participants with 100,000 person years of follow up.

Examples of potential solutions that were discussed included using averted infections ratio, refining the statistical approach in non-inferiority studies to measure time without incidents, using MAMS or using surrogate endpoints (such as incidence of rectal STIs).

C O M M E N T

Given the pipeline for PREP is currently very strong and for vaccines is promising, there might be an urgency for regulatory agencies to show rapid flexibility for new ways to

validate statistical efficacy.

This might even be needed in time for promising compounds that are currently in phase 3 studies if there are fewer events due to either high PrEP efficacy and/or lower HIV incidence that might have dropped while these studies have been running.

These models will also be included in an upcoming multiagency meeting on PrEP design that will be held in Seattle next month. [8]

References

1. McCormack S. Novel trial designs for a complex environment. R4P2018, 21-25 October 2018. Plenary lecture PL 01.02.
<https://www.professionalabstracts.com/hivr4p2018/iplanner/#/presentation/60> (abstract)
<http://webcasts.hivr4p.org/console/player/40303> (webcast)
2. EHVA study. An HIV Vaccine Trial in Individuals Who Started ART During Primary or Chronic Infection (EHVAT01). NCT02972450.
<https://clinicaltrials.gov/ct2/show/NCT02972450>
3. PrEPVac study. A combination effect study in Africa of two DNA-MVA- or DNA- Env protein HIV-1 vaccine regimens with pre-exposure prophylaxis (PrEP).
<https://www.avac.org/trial/prepvacc>
4. Sydes MR et al. Flexible trial design in practice - stopping arms for lack-of-benefit and adding research arms mid-trial in STAMPEDE: a multi-arm multi-stage randomized controlled trial. *Trials* 2012, 13:168. DOI: 10.1186/1745-6215-13-168.
<https://trialsjournal.biomedcentral.com/articles/10.1186/1745-6215-13-168>
5. Gilbert et al. A sequential phase 2b trial design for evaluating vaccine efficacy and immune correlates for multiple HIV vaccine regimens. *Stat Comm Inf Dis* (2011) Oct;3(1). pii: 1037.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3502884>
6. Murray J. Regulatory perspectives for streamlining HIV prevention trials. R4P2018, 21-25 October 2018. Oral abstract SY03.01.
<https://www.professionalabstracts.com/hivr4p2018/iplanner/#/presentation/8> (abstract)
Webcast link to be added when online (webcast)
7. Donnell D. Novel trial design in the era of successful HIV prevention interventions. R4P2018, 21-25 October 2018. Oral abstract SY03.02.
<https://www.professionalabstracts.com/hivr4p2018/iplanner/#/presentation/4> (abstract)
8. HIV Prevention Efficacy Trial Designs of the Future.
<http://www.hvtn.org/en/about/hvtn-conferences/hiv-prevention-efficacy-trials-design-of-the-future.html>

Dual bNAbs treatment maintains viral suppression for median 21 weeks off-ART

Simon Collins, HIV i-Base

In the first presentation in a session looking at using bNAbs for prevention, Pilar Mendoza from the Rockefeller University presented results on the

impact of a combination of two antibodies in HIV positive people on ART who then took an analytic treatment interruption (ATI). [1]

The two bNAbs, 3BNC117 and 10-1074, target non-overlapping epitopes and provide broader coverage. All 11 participants were initially screened for sensitivity to both antibodies (there was an approximate 50% rate of failing screening) and were on effective ART.

ART was stopped two days after the first dual infusion, with additional infusions at weeks 3 and 6 when off ART.

The reservoir was measured at the first infusion and at 12 weeks (when suppressions was still expected) and the criteria to restart ART was two consecutive viral load results >200 copies/mL or at 30 weeks, whichever was sooner.

Viral suppression using the dual bNAbs resulted in median 21 weeks to viral rebound >200 copies/mL, which was significantly longer compared to historical controls or previous single bNAb studies ($p < 0.0003$). Two participants were still virally suppressed at week 30.

However, 2/11 participants were later found to have preexisting bNAb resistance in the viral reservoir that was not detected at baseline, and both responded with similar early viral rebound to monotherapy studies.

Analysis of the time to rebound in the 9/11 sensitive participants showed this closely linked to when plasma levels of 3BNC117 fell below estimated therapeutic concentrations of 10 ug/mL, leaving a window of monotherapy to 10-1074 due to its longer half-life. This also meant that rebound virus tended to show resistance to 10-1074.

Some participants also rebounded after both antibodies were cleared. No cases of double resistance were reported.

No reduction in the viral reservoir was seen between baseline and week 12.

Previous studies using 3BNC117 monotherapy delayed viral rebound by approximately nine weeks.

C O M M E N T

These tentative results show an exciting potential for combination bNAbs therapy to maintain viral suppression off-ART.

However, the rapid rebound with antibody resistance during periods of effective monotherapy is an important caution for future research.

This also creates a challenge for considering pharmacokinetic profiles of different molecules

when used in combinations.

Reference

1. Mendoza P et al. Combination of HIV-1 antibodies 3BNC117 and 10-1074 delays viral rebound during treatment interruption. R4P2018, 21-25 October 2018, Oral abstract OA08.01.
<http://webcasts.hivr4p.org/console/player/40352> (webcast)

Cabotegravir levels can be detected several years: PK tail to be covered by oral PrEP

Simon Collins, HIV i-Base

The properties of long-acting PrEP drugs that reduce the need for daily dosing also presents a new set of challenges if and when people decide to stop.

When LA drugs are used for treatment, this is less of a problem, as HIV positive people will usually be switching to an alternative drug combination.

However, when these drugs are used for PrEP, there will be months - or in some cases years - where there are different concerns from the long time they take to leave the body. In the phase 2 ECLAIR study, 17% of men had detectable cabotegravir levels a year after their final injection of 800 mg IM given on a 12-week schedule.

One presentation at R4P2018 included the most detailed results so far on the variability in the time taken for cabotegravir LA to leave the body during the long “tail” phase.

Final PK results from an earlier HPTN 077 study, using either 600 mg IM Q8W or 800 mg Q12W dosing. Results were presented from the 135/177 participants (33 placebo) who had follow up 76-weeks after the final injection. Results were combined from both arms as no differences were seen on the “tail” PK. Overall, 60% of participants were women.

Individual PK results were presented with reference to protein adjusted IC90 levels and expected levels of protection.

At 60-weeks after the final injection, 23% men and 63% women had detectable cabotegravir levels above the lower limit of quantification (25 ng/mL, LLOQ) which dropped to 13% and 42% at week 76, see Table 1. It was emphasised that at these levels cabotegravir was modelled to still provide >74-80% protection.

In multivariate analysis, factors associated with longer PK tail were female sex at birth [1.45 (95%CI: 1.17 to 1.81) $p=0.001$] and higher BMI per unit increase [1.02 (95%CI 1.01 to 1.04) $p<0.003$]. However, on 17% of the variation was explained by these two parameters.

The median estimated time to LLOQ was 42 weeks (range 20 to 134) for men and 66 weeks (range 17 to 182) for women, but the upper ranges were 2.5 years and 3.5 years for men and women respectively, noted by the session chair to be “rather a long time”.

Phase 3 studies are recommending using oral PrEP for 48 weeks after the last injection although this threshold for risk of developing drug resistance is not yet known. In practice though, people who chose long-acting injections might be those who either cannot or do not want to use oral PrEP.

Table 1: Cabotegravir drug levels after final injection

	Week 60		Week 76	
	Men (n=40)	Women (n=82)	Men (n=30)	Women (n=64)
<LLOQ	78%	37%	87%	58%
LLOQ to <1xPA-IC90	15%	40%	13%	31%
1x to 4 x PA-IC90	8%	23%	0	11%

Key: LLOQ: lower limited of quantifications (<25 ng/mL), PA-IC90 protein adjusted 90% inhibitory concentration.

Reference

Landovitz R. Tail-phase Safety, Tolerability and Pharmacokinetics of Long-acting Injectable Cabotegravir in HIV-uninfected Individuals: HPTN 077 Final Results. Oral late-breaker abstract OA15.06LB.

[http://www.professionalabstracts.com/hivr4p2018/iPlanner/#!/presentation/347\(abstract\)](http://www.professionalabstracts.com/hivr4p2018/iPlanner/#!/presentation/347(abstract))
[http://webcasts.hivr4p.org/console/player/40424\(webcast\)](http://webcasts.hivr4p.org/console/player/40424(webcast))

3D imaging shows HIV infection might establish within hours

Simon Collins, HIV i-Base

A fascinating lecture that generated a lot of discussion at R4P2018 showed how advances in modern scanning technologies including PET scans and light sheet microscopy can be used to get more accurate information about the first stages of HIV infection and on the ways that HIV drugs are absorbed and distributed in the body.

Although this talk used animal studies, the approach is safe enough to use in humans. These might have a role in cure research, for example, to look to measure sites of active HIV replication, before or after a treatment interruption as well as in the

development of new drugs.

Many of the videos, which are fascinating to watch, were shown as 3D models - rotated to view the distributions from any angle - and then guiding accurate biopsies.

The results looked at HIV transmission in used fluorescent stained proteins to track viral particles in explant tissue or in live animals. One unexpected finding was that virus was transported to mesenteric lymph tissue within hours of infection - much sooner than generally assumed. This might have an immediate practical use when modelling PrEP studies.

A second approach, to image drug distribution, can map local absorption of PrEP, for example from a tenofovir vaginal ring, or other topical or system prevention drugs.

As next steps, human imaging that has been discussed for several years is just starting to happen, including in HIV cure research where it has the potential to identify actively productive residual cells.

Reference

Hope TJ. Visualizing HIV transmission and prevention. R4P2018, 21-25 October 2018. Plenary lecture abstract PL02.01.

[http://www.professionalabstracts.com/hivr4p2018/iPlanner/#/presentation/66\(abstract\)](http://www.professionalabstracts.com/hivr4p2018/iPlanner/#/presentation/66(abstract))

[http://webcasts.hivr4p.org/console/player/40307\(webcast\)](http://webcasts.hivr4p.org/console/player/40307(webcast))

bNAbs for HIV prevention: extended-release VRC01, AMP study, 10E8 safety signal and pan-clade challenges

Simon Collins, HIV i-Base

The R4P2018 conference included a wealth of studies looking at broadly neutralising monoclonal antibody (bNAbs) for HIV prevention.

A selection of these studies reported below shows the complexities of this research which is important given large-scale studies are already ongoing.

New data on a long-acting variant of the bNAb VRC01 that requires less frequent infusions was included in several presentations.

This extended release formulation, VRC01-LS, has a two amino acid change that showed more durable protection against repeated SHIV challenges in animal studies.

A talk by Ann Marie Carias from Northwestern University looked to explain the complicated distribution of IV antibodies and the mechanism for the longer half-life of the new molecule.

PK data from VRC01-LS was presented using deconvolution (DV), light sheet microscopy (LSM) and and correlative positron emission tomography (PET) imaging was used to map antibody accumulation of VRC01 and VRC01-LS systemically and in cells and mucosal tissue in rhesus macaques.

Two hours after administration, both VRC01 and VRC01-LS were initially concentrated in the liver, but VRC01-LS accumulation was then more prominent in the transverse colon. At 72 hours, VRC01 is detected in the small intestines while VRC01-LS is largely accumulated in the lungs and large intestines. Importantly, accumulation at one site reduced distribution at other sites.

Carias also reported that antibody distribution varied between different tissue and cellular levels. For example, results at mucosal sites with squamous epithelium (vagina, oral cavity, inner foreskin) were distinct from sites with columnar epithelium (gut, rectum, upper FRT).

VRC01-LS remained longer than VRC01, including in brain tissue, apparently due to endosomal recycling within endothelial cells.

An earlier talk on using VRC01 to protect infants from transmission during breastfeeding also included a PK slide for the VRC01-LS formulation. [2]

Although the babies in these studies are already expected to have very low risk from HIV transmission, the intervention might be important in situations of higher risk, for example, when HIV is diagnosed very late in the pregnancy and before ART reduces viral load.

A second session on using bNAbs later the same day included a presentation from Lynn Morris from the National Institute for Communicable Diseases, South Africa, on the ongoing phase 2b efficacy AMP studies using VRC01 to prevent HIV infection. [3]

These two studies – HVTN703/HPTN 085 in gay men and transgender women in North and South America and HVTN704/HPTN 081 in African women – are now fully enrolled.

VRC01 is given as either a high or low dose (30 vs 10 mg/kg) by IV infusion every two months which results in highest antibody levels at the beginning of each dosing period that gradually drop so that protection also becomes more limited by the time of the next dose.

HIV sub-type is also important. Predicted coverage in the high dose groups include >90% coverage (based on IC80) for both mid-cycle and trough concentrations for subtype B and ~75% for subtype C. In the low dose arm, this coverage remains high for mid-cycle levels but drops to only 82% protection at the trough level for clade B. For sub-type C, mid-cycle protection is only 73% and end-of-cycle trough levels drop to only 58% predicted coverage. See Table 1.

Table 1: Predicted coverage of VRC01 for HIV prevention based on in vitro neutralisation levels

	% breadth coverage (IC80)	
	Clade B	Clade C
<i>High dose (30 mg/kg)</i>		
Midpoint (30 ug/mL)	93	75
Trough (16 ug/mL)	93	73
<i>Low dose (10 mg/kg)</i>		
Midpoint (16 ug/mL)	93	73
Trough (4 ug/mL)	82	58

Although using monotherapy with a single bNAb is already expected to lead to breakthrough infections due to limited potency and breadth of coverage, with perhaps important differences based on HIV clade, the AMP study plans to investigate mechanisms of protection and failure.

The presentation also included details about patterns of drug resistance to VRC01 (at positions 456, 459, 270 and others) and the impact on drug sensitivity. This might lead to a genotypic predictive score that might replace the current need for neutralisation sensitivity screening at baseline.

An update on current enrollment in the AMP studies was presented by Sri Edupuganti from Emory Vaccine Research Center in an excellent satellite session organised by the HIV Prevention Trials Network and HIV Vaccine Trials Network. [4, 5]

Also related, the following day, Jeffrey Schneider from Northwestern University, gave a talk showing that the VRC01 takes approximately a week to achieve steady-state in vaginal tissue in animal models, with gradual trafficking from plasma to tissue. [6]

Distribution to rectal tissue appears to be take a similar time for steady state levels, but delivered by cellular rather than vascular mechanism. Clarified tissue from 27 organs showed differential distribution through different transport mechanisms, again showed in impressive 3D imaging.

Several pipeline combinations of dual and triple antibodies are already being studied including VRC07 + PGDM1400 + PGT 121) in HVTN130/HPTN 089. A tri-specific engineered molecule with three specificities on one antibody (VRC01/PGDM1400/10E8) is also being studied in HVTN129/HPTN 088.

The difficulties of pan-clade activity even with combination antibodies is an important limitation to their efficacy for prevention on both an individual and population level.

Bette Korber from the Los Alamos National Laboratory reviewed the challenges of combining antibodies for global HIV prevention emphasising the differences by clade in the same HVTN and HPTN satellite session and related paper. [7] The modelling in a related paper suggests that nearly complete neutralisation of a given virus is needed for in vivo protection (~98% neutralisation for 50% relative protection) and that the inclusion of 10E8 is likely important to provide cross-clade protection in African studies. [8]

Korber outlined the importance of avoiding virtual monotherapy and that pan-clade coverage requires two, three or four bNAbs to ensure two or more active molecules. The talk emphasised that global studies needed to select antibody combination based on clade prevalence in the countries where the research is being conducted, with a comment that while AMP studies will provide important results, the clinical benefits are likely to be less than optimal.

However, while the safety and tolerability of bNAbs are generally good, grade 3 skin erythema was reported to 10E8 study in 7/8 participants in an early study. Reactions occurred two days after receiving dual 10E8LS and VRC07 infusion (separately to each side of the stomach). These were associated with mild tenderness and fever (both transient) and confirmed by biopsy as panniculitis with lymphocytic inflammation (all cases resolved). This has been sufficient to put further clinical development of 10E8 on hold, although the implications for the triple and trispecific studies were not provided. [9]

C O M M E N T

Although the longer half-life of VRC01-LS improves dosing, it is unclear whether it would overcome the vulnerability from use as single antibody monotherapy by sustaining higher drug levels – though this seems unlikely.

From an advocacy perspective, these presentations suggests the importance of encouraging study participants in the ongoing phase 2b Antibody Mediated Protection (AMP) HIV prevention studies to also use oral PrEP, at least in countries where this is available. The data on time to steady-state is also important for these participants.

Results from the pivotal proof of concept AMP studies are expected within two years.

Reference

1. Carias AM et al. Imaging the distribution of I.V.-injected VRC01 and VRC01-LS in the in vivo rhesus macaque model. R4P2018, 21-25 October 2018. Oral abstract OA08.06.
<https://www.professionalabstracts.com/hivr4p2018/iplanner/#/presentation/326> (abstract)
<http://webcasts.hivr4p.org/console/player/40357> (webcast)
2. Cunningham C et al. Safety and pharmacokinetics of multiple doses of a potent anti-HIV monoclonal antibody VRC01 in HIV-exposed newborns. R4P2018, 21-25 October 2018. Oral abstract OA08.05.
<https://www.professionalabstracts.com/hivr4p2018/iplanner/#/presentation/256> (abstract)
<http://webcasts.hivr4p.org/console/player/40356> (webcast)

3. Morris L et al. Antibody mediated protection (AMP): where are we? which antibodies to use and how will we know if it's working? R4P2018, 21-25 October 2018. Oral abstract SY01.02.
<https://www.professionalabstracts.com/hivr4p2018/iplanner/#/presentation/42> (abstract)
<http://webcasts.hivr4p.org/console/player/40359> (webcast)
4. Edupuganti S et al. Where are we in AMP Trial? R4P2018, 21-25 October 2018. HVTN and HPTN satellite session. 21 October, 4.00 pm.
<http://webcasts.hivr4p.org/console/player/40528> (webcast)
5. HIV Vaccine Trials Network and HIV Prevention Trials Network. State of the art of HIV bNAbs for prevention of HIV infection. R4P2018, 21-25 October 2018. Satellite session SA04.
<http://www.professionalabstracts.com/hivr4p2018/iplanner/#/grid> (abstract)
6. Schneider J et al. Tracking Cy5-conjugated VRC01 following IV injection in the rhesus macaque reveals that tissue distribution can take 1 week to achieve steady state. R4P2018, 21-25 October 2018. Oral abstract O9.05.
<https://www.professionalabstracts.com/hivr4p2018/iplanner/#/presentation/325> (abstract)
<http://webcasts.hivr4p.org/console/player/40383> (webcast)
7. Korber B et al. Modelling coverage with combination monoclonals: the 2 vs. 3 issue. HVTN and HPTN satellite session. 21 October, 4.00 pm.
<http://webcasts.hivr4p.org/console/player/40530> (webcast)
8. Wagh K et al. Potential of conventional & bispecific broadly neutralizing antibodies for prevention of HIV-1 subtype A, C & D infections. PLoS Pathogens (2018). DOI: 10.1371/journal.ppat.1006860.
<https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1006860>
9. Koup R. Review of bNAbs in clinical development. R4P2018, 21-25 October 2018. HVTN and HPTN satellite session. 21 October, 4.00 pm.
<http://webcasts.hivr4p.org/console/player/40515>

Why U=U does not cover breastfeeding

Simon Collins, HIV i-Base

One of the last sessions at R4P2018 included six talks about U=U, one of which reviewed the evidence about breastfeeding. This is important because rather than just sexual transmission, U=U is sometimes wrongly interpreted as covering all ways that HIV can be transmitted.

Lena Serghides from University Health Network and University of Toronto answered the opening question of whether ART eliminates HIV transmission with a clear “no”. While it is easy to show that ART dramatically reduces the risk for all routes of transmission, it is only sexual transmission where the risk is proven to be effectively zero. [1]

This talk emphasised that cases of HIV transmission have already been reported when mothers are on ART with undetectable viral load, notably in results from the PROMISE trial. Latest results presented at AIDS 2018 reported that 2/8 cases when transmission occurred from breastfeeding were in women whose most recent viral load was <40 copies/mL. [2]

So although HIV treatment dramatically reduces the risk of transmission during breastfeeding, the risk is not zero. None of the studies looking at this risk have reported a zero result, with a meta analysis that drove WHO guidelines reported risk of 1.1% and 2.9% with 6- and 12-months breastfeeding in mothers on ART. [3]

Possible reasons for risk not becoming zero

Possible explanations for this residual risk include:

- High lifetime exposure volume compared to sexual fluid: 3-4 cups of milk a day is 150 litres over six months.
- Breast milk is likely to include 1 million immune cells/day and 150 million over six months.
- Breast milk induces immune activation and HIV replication is 10-fold higher in milk vs blood.
- Cell associated HIV DNA persists on ART and latently infected resting cells are transmitted (and then activated) in milk.
- Breast inflammation can activate HIV (mastitis, abscess, engorgement etc).
- Great immune vulnerability in infant GI tissue.
- Adherence difficulties post partum (erratic sleep, depression, support) are well documented in all settings, including high-income countries. [5]

Breastfeeding starts off with a much higher risk of transmission because the infant is exposed to far higher amounts of infectious fluid.

Context: low- vs high-income settings

Crucially, context for risk drives current WHO recommendations.

In low-income settings with limited access to clean water, formula feed and medical care the recommendation to breastfeed on ART means the positive benefits from breast milk in fighting malnutrition, diarrhoea and pneumonia outweigh the low risk of HIV transmission.

In high-income settings where the rates of infant mortality from background health risks are much lower, the recommendation to use formula feed has the best outcome in terms of infant health and the higher risk comes from HIV via breastfeeding.

C O M M E N T

This is an area where more data on transmission risk from mothers on ART will become increasingly available now that the WHO recommends both continued ART

and breastfeeding in low income countries. Earlier evidence reviews on risk showed heterogeneity of approaches with many studies not fully reporting timing and use of ART and importantly, maternal viral load data.

Prospectively collecting cases in large observational databases, similar to the approach in the PARTNER studies for sexual transmission, is not only ethical, but essential.

Although a recent discussion paper from some of the doctors involved in the original Swiss Statement, suggested there might be equipoise on risk for women in high-income countries, this was published before the cases were presented from the PROMISE study.

Currently, National guidelines, including in the UK (and Switzerland), continue to recommend that the safest option for the baby in high-income countries is to use formula feed and not to breastfeed. [6]

References

1. Serghides L. What Does U=U Mean for Breastfeeding? R4P2018, 21-25 October 2018, Oral abstract R2.03.
<http://www.professionalabstracts.com/hivr4p2018/iPlanner/#/presentation/31> (abstract)
<http://webcasts.hivr4p.org/console/player/40493> (webcast)
2. Flynn P et al. Association of maternal viral load and CD4 count with perinatal HIV-1 transmission risk during breastfeeding in the PROMISE postpartum component. AIDS 2018. Amsterdam. 23–27 July 2018. Poster abstract THPBE155.
<http://programme.aids2018.org/Abstract/Abstract/4897> (abstract)
3. Bispo S et al. Postnatal HIV transmission in breastfed infants of HIV-infected women on ART: a systematic review and meta-analysis. J Int AIDS Soc. 2017 Feb 22;20(1):21251. doi: 10.7448/IAS.20.1.21251.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5467610>
4. Kahlert C et al. Is breastfeeding an equipoise option in effectively treated HIV-infected mothers in a high-income setting? Swiss Medical Weekly, 148:w14648, 2018.
<https://smw.ch/en/article/doi/smw.2018.14648>
5. Huntington S et al. UK Collaborative HIV Cohort (UK CHIC) Study and the UK and Ireland National Study of HIV in Pregnancy and Childhood (NSHPC). The risk of viral rebound in the year after delivery in women remaining on antiretroviral therapy. AIDS. 2015;29(17):2269–78. doi: 10.1097/QAD.0000000000000826.
https://journals.lww.com/aidsonline/fulltext/2012/10230/Adherence_to_antiretroviral_therapy_during_and.6.asp
6. BHIVA. Management of HIV infection in pregnant women 2018 - Consultation version.
<https://www.bhiva.org/guidelines>
<https://www.bhiva.org/file/WrhWAPoKvRmeV/BHIVA-Pregnancy-guidelines-consultation-draft-final.pdf> (PDF)

ANTIRETROVIRALS

FDA updates rilpivirine label for use during pregnancy

Simon Collins, HIV i-Base

On 31 October 2018, the US FDA approved changes to the label for fixed dose combinations (FDC) containing rilpivirine: Odefsey (RPV/FTC/TAF) and Eviplera/Complera (RPV/FTC/TDF).

For pregnant patients who are already on an RPV-based FDC prior to pregnancy and are virologically suppressed (HIV-1 RNA less than 50 copies/mL), one tablet, once daily may be continued.

Lower exposures of rilpivirine were observed during pregnancy, therefore viral load should be monitored closely.

A similar recommendation was recently made for rilpivirine (RPV) (trade name Edurant) as a single ARV.

Source:

FDA list serve update (31 October 2018)

GUIDELINES

EACS guidelines update (2018)

Simon Collins, HIV i-Base

The 2018 update to the European guidelines for treatment of HIV-positive adults in Europe is now available online and as a PDF file.

Currently, online the English edition - version 9.1 - is available but translations into additional languages will be published later as they become available.

These include Chinese, French, German, Portuguese, Russian Spanish and Japanese (currently online as version 9.0 from 2017).

The changes to the 2018 edition are also helpfully summarised on the first page.

These include:

- Adopting integrase inhibitor-based ART (but not elvitegravir) as first-line therapy, although boosted darunavir is also included as preferred option.
- Downgrading elvitegravir to an alternative option.
- Including recently approved drugs like bictegravir, TAF and once-daily raltegravir.
- Including the two-drug combination of dolutegravir + lamivudine as an alternative option (if viral load is <500,000)
- Dolutegravir (during first trimester), raltegravir 1200 mg, bictegravir, and darunavir/cobicistat are no longer recommended during pregnancy.
- Drug interactions have been included for newer drugs.
- Smaller changes have also been made to the sections on management of TB, hepatitis and other opportunistic infections.

Links

EACS guidelines (2018)

www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html

www.eacsociety.org/files/2018_guidelines-9.1-english.pdf (PDF)

Summary of changes from v 9.0 to v 9.1 editions.

www.eacsociety.org/files/guidelines_changes_from_v9.0_to_v9.1.pdf (PDF)

TB COINFECTION

Activists demand \$1 a day access to bedaquiline for MDR TB

MSF press release

On 24 October 2018, activists interrupted the opening ceremony of the 49th Union World Conference on Lung Health in The Hague, to call on US pharmaceutical corporation Johnson & Johnson (J&J) to cut the price of the TB drug bedaquiline in half, to 'one dollar per day', so that people who urgently need it can afford it.

The World Health Organization (WHO) recently recommended expanding the use of the newer oral drug bedaquiline (produced by J&J), making it a core drug for treatment of drug-resistant tuberculosis (DR-TB), while relegating to last resort those TB drugs that need to be injected and cause horrible side effects. These new treatment guidelines more than double the number of people with DR-TB for whom bedaquiline treatment is recommended. Governments must act fast to expand access to bedaquiline as a core component of safer, more effective, injection-free treatment regimens.

J&J recently reduced the price of bedaquiline to US\$67 per person per month (US\$400 per six-month course). However, this price falls short of making the drug affordable in countries that are hardest hit by DR-TB, especially given that bedaquiline is just one of up to seven medicines that are necessary to compose a treatment regimen for DR-TB, and considering many people will need to take bedaquiline for longer than six months.

At \$67 per month, bedaquiline is more than double the price of linezolid (\$29–42 per month) and up to 22 times the price of levofloxacin or moxifloxacin (\$3–9 per month), the two other medicines the latest WHO treatment guidelines recommend for the backbone of DR-TB treatment regimens. However, researchers from the University of Liverpool have calculated that bedaquiline could be produced and sold at a profit for \$16 per month at volumes of 108,000 treatment courses per year.

Activists today demanded that J&J cut the price of bedaquiline in half, to no higher than \$1 per day—\$32 per person per month—double the price that researchers estimate bedaquiline could be sold for a profit. Doubling the price is intended to account for current low volumes—only 25% of the 558,000 people estimated to have developed MDR-TB in 2017 were started on treatment, and most did not receive bedaquiline. To date, only 25,000 people have received bedaquiline worldwide.

Groups pointed to the significant taxpayer money that J&J has received for the development and introduction of bedaquiline, and the need for these public investments to be reflected in the price of the drug.

Source

MSF press release. Activists interrupt TB conference opening ceremony to call on J&J to cut price of TB drug in half, to one dollar per day. (24 October 2018)

<https://msfaccess.org/activists-interrupt-tb-conference-opening-ceremony-call-jj-cut-price-tb-drug-half-one-dollar-day>

OTHER NEWS

Cannabis-based products for medicinal use: Guidance to clinicians

Simon Collins, HIV i-Base

Following the Government's announcement to reschedule certain cannabis-based products for medicinal use, NHS England has provided guidance to clinicians following the re-scheduling. [1]

The document – published on 31 October 2018 – sets out expectations of what this regulatory change will mean in practice for clinicians working in the NHS and in private practice in England.

C O M M E N T

This slight loosening of restrictions to cannabis-based products for medical use doesn't change legality of cannabis itself.

The document notes that dronabinol – an appetite stimulant that was available in the US decades ago and used for HIV-related wasting – is still not available in the UK.

On the same day, the Mexican Supreme Court ruled that the prohibition of cannabis was unconstitutional - as it violated the 'fundamental right to the free development of the personality'.

This has effectively legalised cannabis for personal use, possession, private cultivation, and sharing of cannabis amongst adults. [2]

NICE guidelines on cannabis-based compounds have also just been published in draft form online: deadline for comments is Tuesday 4 December 2018. [3]

References

1. NHS. Guidance to clinicians: Cannabis-based products for medicinal use (31 October 2018). <https://www.england.nhs.uk/publication/cannabis-based-products-for-medicinal-use-guidance-to-clinicians>
2. Transform. Press release. Mexican Supreme Court Ruling Means Recreational Cannabis is Now Legal for Adults. (01 November 2018). <https://www.tdpf.org.uk/blog/press-release-mexican-supreme-court-ruling-means-recreational-cannabis-now-legal-adults>
3. NICE. Cannabis-based products for medicinal use. Draft for comments. <https://www.nice.org.uk/guidance/indevelopment/gid-ng10124/consultation/html-content>