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EDITORIAL

This issue of HTB continues our reports from the 22nd International AIDS Conference (AIDS 2018) that was held from 23–27 July 2018 in Amsterdam.

We start with the optimistic news that Namibia is already close to achieving the 90-90-90 goals – with results presented by the Namibian Minister of Health at the conference.

Less optimistically, two studies showed results from using dolutegravir monotherapy, which, at least from the audience's response, should not be continued due to the risks of unpredictable viral rebound.

We also use this issue to highlight several posters from the conference covering changing comorbidities in a UK ageing cohort, use of digital (finger, not electronic) monitoring for HPV, high rates of HPV in a PrEP cohort, and high incidence of HCV reinfection (also in a PrEP cohort.

We include a review of cure-related studies, two studies about increasing access to viral load testing, and a UK protocol for helping diagnose people whose HIV test results are repeatedly indeterminate.

An additional report from the paediatric workshop reviews a new dispersible tablet formulation of dolutegravir for children.

Antiretroviral news includes top-line results from the phase 3 ATLAS study, bringing long-acting, injectable ART a little closer and new FDA updates on interactions between anticoagulants and Genvoya, Stribild and cobicistat.

We include sobering news on continued rates of death to drug overdoses, especially to opiates and recreational drugs.

And we end with new resources from the Martin Fisher Foundation that include online videos to reduce HIV-related stigma.

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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

22nd International AIDS Conference (AIDS 2018)

23 – 27 July 2018, Amsterdam

Introduction

The 22nd International AIDS Conference (AIDS 2018) was held this year from 23–27 July in Amsterdam.

Several thousand studies were presented as oral lectures or exhibited as posters over four days - so all reports touch on a minority of the research and activity - but much of the conference is also available online.

- Abstracts are online using a searchable database for the conference programme.

  http://programme.aids2018.org

  Clicking on a search result opens a separate window, either for the abstract or the session in which it was presented.
- Slides are available for most oral presentations and plenary lectures.
- Webcasts are available for many oral presentations (using the "video" link in the session window).
- Posters are available for many abstracts (using a PDF download link at the bottom of the abstract window).
- Oral abstracts are also available online and as a PDF supplement to JIAS.

  https://onlinelibrary.wiley.com/doi/full/10.1002/jia2.25148

Reports included in this issue of HTB.

AIDS 2018: GLOBAL ACCESS

Namibia close to achieving 90-90-90 targets

Polly Clayden, HIV i-Base

Namibia is the first African country to have reached and overtaken the UNAIDS 2020 goal to have at least 73% of HIV positive adults virally suppressed – these findings from the Namibia Population-based HIV Impact Assessment (NAMPHIA) were presented at AIDS 2018.

In terms of 90-90-90 targets, this overall proportion represents 86% of people with HIV who reported knowing their status; 96.4% of those on ART; and 91.3% of those treated virally suppressed to <1000 copies/mL. Women in Namibia have achieved the UNAIDS targets with positive implications for both sexual and vertical transmission.

According to UNAIDS 2015 data, the population of Namibia was less than 2,500,000, with HIV incidence of 0.8% and prevalence of 14% – just over half of the population live in rural areas.

Since 2014 Namibia has implemented extensive scale up of national HIV prevention and treatment services. Between 2015 and 2017 the number of HIV tests administered, new HIV cases identified and people started on ART almost doubled. In 2017 approximately 186,000 people with HIV were receiving ART.

NAMPHIA was a cross-sectional household-based survey (two stage cluster sample design), conducted between June and December 2017 powered to estimate national HIV incidence as well as national and regional prevalence of viral load suppression <1000 copies/mL.

The sample was weighted to account for complex survey design. Eligible adults aged 15–64 years who consented were interviewed and offered rapid HIV testing according to national guidelines. All HIV positive samples were tested for viral load at a central laboratory. Samples were also tested for presence of ARVs (efavirenz, lopinavir/ritonavir and nevirapine).

The total respondents (23,700) included 16,939 adults and 6,761 children. Overall response rate was 67%; 71% of women, 62% men and 73% children ages 0–14 years.

Among the 16,939 adults, total HIV prevalence was 12.6%; female 15.7% and 9.3%. Prevalence peaked at 30% in women

aged 45–49 years. By region HIV prevalence ranged from 7.6 to 22.3%. The highest prevalence was in the Zambezi region – presenting author Bernard Haufiku, Minister of Health and Social Services, noted this part of Namibia borders four other countries and there is a lot of cross border migration for work. He also noted that the regions with the lowest prevalence also had the highest rates of traditional circumcision.

Total HIV incidence was 0.4% (half that reported in 2015); 0.56% among women and 0.15% among men.

Among all HIV adults with viral load results, 77.4% were virally suppressed; 81.7% of women and 69.6% of men. The highest rates of viral suppression were in the 55–64 years age group; 93.5% women and 86.28% men. The lowest was among adolescents and young adults with only 50.5% of men aged 25–34 years achieving viral suppression.

By region viral load suppression ranged from 55.2% to 86.2%; higher rates of suppression were in regions with higher prevalence of HIV.

The total 90-90-90 cascade was close to full achievement of UNAIDS targets: 86.0%, 96.4% and 91.3%, of people diagnosed, on ART and virally suppressed respectively (adjusted for detectable ARVs). These proportions were 89.5%, 97.1% and 92.2% for women; and 79.5%, 94.9% and 89.5% for men. These were highest among people 55–64 years of age.

Once diagnosed, over 90% of men and women are linked to ART services and are virally suppressed. But many HIV positive adolescents and young adults do not know their HIV status.

Overall 14% of all HIV positive people do not know their status and strategies to improve HIV testing, particularly for men, are urgently needed to ensure Namibia's continued impressive progress towards HIV epidemic control.

Bernard Haufiku concluded: "NAMPHIA data shows historic success and can also direct our programming to where it needs to be". He added that there is: "No time to relax and no place for complacency, [these findings] should put an extra spike of energy into our programme".

Reference

Hamunime N et al. Progress toward HIV epidemic control: Results from the Namibia Population-Based HIV Impact Assessment (PHIA). AIDS 2018. Amsterdam. 23–27 July 2018. Oral abstract THAC0408LB.

http://programme.aids2018.org/Abstract/Abstract/13468 (abstract)

https://www.youtube.com/watch?v=kPGD7ErMNQc (webcast)

AIDS 2018: ANTIRETROVIRALS

Dolutegravir monotherapy: still no longer recommended in either research or clinical practice

Simon Collins, HIV i-Base

Although in 2015 several research groups reported promising early results from small studies using dolutegravir (DTG), these studies were generally stopped due to the unpredictability of viral rebound in some participants. The cases involved a high likelihood of cross-class integrase inhibitor drug resistance. [1, 2]

This led to universal recommendations in treatment guidelines in 2016 (UK, US, EACS) against further research into the use of dolutegravir monotherapy.

It was therefore disconcerting to have two oral presentations at AIDS 2018 reporting studies that still continued after these guidelines recommendations, one of which plans to continue follow-up out to four years.

The first was a French switch study called MONCAY, presented by Laurent Hocqueloux from the Regional Hospital of Orléans, which included an analysis of virological failures on dolutegravir monotherapy, that rightly led to the study being stopped, but long after other studies should have already alerted researchers to this danger. [3]

MONCAY randomised 158 virally suppressed participants on DTG/3TC/abacavir to either switch to dolutegravir monotherapy or remain on triple-drug ART. Baseline demographics (in the monotherapy arm) included median CD4 nadir of 309 cells/mm^3, current CD4 843 cells/mm^3, time since diagnosis 9.5 years, median time on ART 8.1 years and use of four previous ART combinations. No IQR or range was provided for these figures.

Five participants using dolutegravir monotherapy had virological failure: two at the week 24 primary endpoint, two at week 36 and one at week 48. Two of these later cases included development of integrase inhibitor mutations. This study started in December 2015 and the DSMB recommended changes in December 2017.

A second study that is worryingly still ongoing was presented by Dominique Laurent Braun from University Hospital Zurich as an oral presentation in the same programme session. [4]

This is an open-label non-inferiority design, that randomised (2:1) 101 participants who were diagnosed within six months of likely HIV infection, to either dolutegravir monotherapy (n=68) or standard triple-drug ART (n=33). Participants had to have been suppressed on ART for >48 weeks. The study started in November 2015 and continued to enrol until March 2017.

Baseline characteristics overall included median age 42 (IQR: 33 to 47), 97% male, 3-6 years (IQR: 1.9 to 8.0) on ART before the study and median CD4 nadir 358 cells/mm3 (IQR: 265 to 486).

One participant in the dolutegravir monotherapy group experienced viral failure at week 36 (with viral load at 382 copies/mL) and two participants in the cART group left the study before the week 48 primary endpoint, because they moved to another country. All remaining participants reported viral load <50 copies/mL at week 48.

Results from a CSF substudy (lumber puncture samples were taken at baseline and week 48; n=23 monotherapy and n=14 triple therapy) were detectable, but at <40 copies/mL, with no difference between the mono and triple therapy groups.

The case of virological failure resuppressed <50 copies/mL after switching back to triple therapy, without development of drug-related resistance. The failure of treatment however, was explained by the researchers as being a protocol violation, due to later discover that primary HIV infection had been incorrectly diagnosed, and that this participant was diagnosed in 2004 as a late presenter.

It was disconcerting when the presenter concluded that dolutegravir monotherapy was an effective and safe option due to showing statistical non-inferiority, with the main concern being accurate diagnosis of acute infection (see comment below).

C O M M E N T

These two presentations generated many audience comments and questions, many focused on the risks for these participants. These are also included on the conference webcasts.

Although one study is now closed (questionably late), it is a concern to hear that ethical consent has been provided for the Swiss study to continue follow-up using monotherapy for up to four years.

This group justified continuing their study because early HIV infection is associated with a smaller reservoir. However, the case of viral failure did not have the highest reservoir, measured by total HIV DNA. Although median reservoir size is lower in acute infection, the range of value commonly show some people having significantly higher HIV DNA levels in acute infection than others have in chronic infection.

Another comment, included the point that non-inferiority studies should now have tighter margins for viral failure, using new FDA recommendation of –4% for the confidence interval (rather than previous use of –10% or –12%).

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AIDS 2018: COMPLICATIONS

Changing comorbidities in HIV positive people older than 60 at London clinic

Simon Collins, HIV i-Base

A retrospective review comparing the changing practice at a large London clinic between 2010 and 2017, highlighted the changing needs and concerns for older people living with HIV.

In 2010, approximately 5% of the cohort at Guys and St Thomas in London (126/2700) were older than 60 and by 2017 this increased to 9% in (300/3299) - nearly doubling over seven years. The results were presented in a poster at AIDS 2018, by Ming Lee and colleagues.

Of the people included in 2010, two-thirds (67%) were still in care; with seven lost to follow up (5%), 13 transferred care (10%) and 21 who had died (16.7%). Causes of death include malignancy (8), HIV-related complications (3), sepsis (2), motor neurone disease (1) or was not available (7).

There were no differences between the timepoints in terms of median age or CD4 count, or in demographics like race, gender or sexuality. ART use had increased with >99% patients (299/300) on ARVs in 2017 compared to 94% (119/126) in 2010.

Prevalence of comorbidities had changed significantly however for people >60, with chronic kidney disease (CKD) affecting 30% of the cohort in 2017 compared to 15% in 2010 (p=0.001) and osteopenia/osteoporosis affecting 36% in 2017 compared to 21% in 2010 (p=0.002). More than half the cohorts at each time had hypercholesterolaemia. In 2017, 44% had hypertension, 16% had a history of malignacy and 4% had heart failure (defined as <55% left ventricular fraction). In 2017, 30% had more than three comorbidites compared to 22% in 2010, though this increase was not statistically significant (p=0.07).

Further information on CKD included greater median time on tenofovir DF (median 65 vs 80 months overall, p=0.035) with a trend linking CKD to TDF, after adjusting for age, ethnicity, diabetes and hypertension (p=0.08).

Older age was associated with use of >5 drugs for comorbidities (29%) with at least one potential drug-drug interactions in half of these patients.

The study concluded that part of the increases in fatty liver disease, renal dysfunction, and osteopenia/osteoporosis might reflect improved monitoring in line with updated national guidelines. However, the high rates of multiple co-morbidities,

polypharmacy and drug interactions required regular ARV reviews for this older population.

Table 1: Prevalence of comorbidities in 2010 and 2017

Comorbidities	2010 (n=126)		2017 (n=300)		p-value
Ischaemic heart disease	22	17.5%	28	9.3%	0.021
Chronic kidney disease stage 3 or worse (CKD3+)	20	15.9%	91	30.3%	0.001
Osteopenia/ osteoporosis	27	21.4%	110	36.7%	0.002
Hypercholesterol-aemia	65	51.6%	171	57.0%	0.336
Diabetes mellitus (Type 1 or 2)	14	11.1%	42	14.0%	0.529
Hypertension	–	–	132	44.0%	–
Heart failure (left ventricular ejection fraction <55%)	–	–	12	4.0%	–
Malignancy	–	–	50	16.7%	–
>3 of above comorbidities	28	22.2%	92	30.7%	0.077

Reference
Lee MJ et al. Beyond the 60s: Changing co-morbidities in people living with HIV aged over 60 attending clinic in 2010 and 2017. AIDS 2018, 23-27 July 2018, Amsterdam. Poster abstract TUPEB136.

http://programme.aids2018.org/Abstract/Abstract/3843

High acceptability of annual digital (finger) exam for early detection of anal cancer in gay men >35 years old

Simon Collins, HIV i-Base

A poster from a prospective Australian cohort study reported that incorporating simple digital anorectal examinations (DARE) – using a finger – into routine HIV care improved clinical outcomes over two years and had high patient acceptability.

The results were presented as a poster at AIDS 2018 by Jason Ong from LSHTM.

The cohort included 327 HIV positive gay men aged above 35 years from a sexual health centre (n=187), two GP surgeries (n=118) and a tertiary hospital (n=22), all in Melbourne. Median age was 59 (SD +/–8) years, 69% were Australian born, 32% current smokers, and mean CD4 was 630 (SD+/–265) cells/mm^3.

Overall, 232 men (71%) received three exams (at baseline and years 1 and 2), 71 (22%) recieved two and 24 (7%) had one result.

Of 862 DAREs performed, 33 (3·8%) examinations resulted in a referral to a colorectal surgeon, see Table 1. One stage 1 anal cancer was detected. The most common incident diagnoses were skin tags, haemorrhoids, warts, fissures and enlarged prostate.

Of 241/327 mean (71%) men who completed the final questionnaire, 95% (229/241) would continue to have an annual DARE beyond the study, and 79% (190/241) felt more likely to consult a doctor if they found an abnormality or had anal symptoms.

This study concluded that integrating an early cancer detection programme into routine HIV clinical care is feasible, especially in settings where anal cytology and high-resolution anoscopy services are unavailable. Although referral rates for surgery remained low over the two years, the involvement of HIV doctors in early anal cancer detection could help with early detection which in turn is associated with better outcomes.

Table 1: Frequency of abnormalities and referrals

	Baseline	**Year 1**	**Year 2**
No abnormality	241 (71%)	214 (80%)	209 (78%)
Anbormality, no referral	69 (22%)	50 (19%)	46 (17%)
Abnormality, with referral	17 (5%)	4 (1%	12 (5%)

Reference

Ong J et al. Early detection of anal cancer in men who have sex with men (MSM) living with HIV by incorporating digital anorectal examinations (DARE) into routine HIV care: A prospective cohort study. AIDS 2018, 23-27 July 2018, Amsterdam. Poster TUPEB083.

http://programme.aids2018.org/Abstract/Abstract/4109

High rates of anal HPV infection in gay men using PrEP: the role of vaccination

Simon Collins, HIV i-Base

A sub study of the high-profile French PrEP study IPERGAY has reported alarmingly high rates of HPV infection in HIV negative gay men.

Preliminary results were presented in a poster at AIDS 2018, by David Veyer and colleagues, categorised by HPV genotype and body site. Longitudinal follow-up is planned, but still ongoing.

This sub study was open to all participants and enrolled 162/414 (37%). Anal, oral and genital swabs were taken at baseline and every six months during two years of follow-up for HPV genotyping (19 high-risk and 9 low-risk). Anal cytology samples were obtained at baseline and at 18/24 months, with results classified as normal or abnormal (ASCUS, LSIL, HSIL, and ASC-H).

Baseline demographics for the sub study included median age 34 years (IQR: 27 to 41), with median of 34 partners in previous two months (IQR: 27 to 41), and median of having sex 10 times in the previous month (IQR: 6 to 20).

More than 90% of the baseline anal samples showed any HPV genotype, with 76% of samples having >1 HPV infection. Presence of any high-risk genotype was 84% in anal tissue, 25% in genital tissue and 10% in oral tissue. Median (IQR) number of high-risk infections was 3 (1 to 4), 2 (1 to 3) and 1 (1 to 2) in each of the three sites respectively, see Table 1.

Although abnormal cytology results were reported for two-thirds of participants, and were associated with higher numbers of HPV infections per individual, this association was not considered significant due number of analyses performed. Overall, 4.5% of cytology results (n=7) were high-grade squamous intraepithelial lesions (HSIL).

Longitudinal data will be presented in the full analysis. No information was included in the poster about clinical treatment.

Table 1: Distribution of HPV genotypes by body site (n=162)

	Anal	Genital	Oral
Analysed samples/total samples (%)	146/157 (93%)	115/161 (71.4%)	156/159 (98.1%)
Any HPV genotype - % (95% CI)	92% (87-96)	32% (23-41)	12% (7-17)
>1 HPV genotype - % (95% CI)	76% (69-83)	17% (10-25)	3% (0.4-6)
Median no. of HPV genotypes (IQR)	4 (2-6)	2 (1-3)	1 (1-2)
Any HR HPV genotype - % (95% CI)	84% (78-90)	25% (17-33)	10% (6-15)
>1 HR HPV genotype - % (95% CI)	62% (54-70)	13% (7-20)	3% (0.1-5)
Median no. of HR HPV genotypes (IQR)	3 (1-4)	2 (1-3)	1 (1-2)
Any LR HPV genotype - % (95% CI)	68% (60-75)	11% (6-17)	3% (0.4-6)
More than 1 LR HPV genotype - % (95% CI)	34% (27-42)	4% (1-8)	1% (0-3)
Median no. of LR HPV genotypes (IQR)	2 (1-2)	1 (1-2)	1 (1-2)
HR HPV genotypes included in vaccine* - % (95% CI)	38% (33-42)	36% (25-48)	41% (20-61)
LR HPV genotypes included in vaccine* - % (95% CI)	26% (20-32)	21% (3-39)	33% (3-64)

* Gardasil 9® (MSD; HPV 6; 11; 16; 18; 31; 33; 45; 52; 58)

C O M M E N T

These data show the importance for young gay men to be broadly informed and aware of the option in the UK to free HPV vaccination on the NHS. This programme extends to men up to 45 years old.

Several recent open access papers present similar incidence data for gay men in the UK, highlighting that oral HPV should be considered as a distinct infection and that sensitivity to high-risk genotypes shows the important likely efficacy of widespread vaccination for gay men. [2, 3]

Reference

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HCV incidence and reinfection in HIV negative gay men using PrEP in the Netherlands

Simon Collins, HIV i-Base

A Dutch PrEP study has reported HCV incidence in HIV negative men that is comparable to previous reports in HIV positive men and with very high rates of HCV reinfection.

Elske Hoornenborg and colleagues reported 12 incident HCV infections (6 new and 6 reinfections) in a cohort of 374 gay men in the Amsterdam PrEP project from August 2015 to December 2017, with a median follow-up of 1.76 patient years (PY) (IQR: 1.57 to 1.98).

This produced an overall incidence rate (IR) of 1.9 per 100 PY (95%CI: 1.1 to 3.4), with IR 1.0/100 PY for incident infections but 25.5/100 PY (95%CI: 11.5 to 56.8) for HCV reinfection.

Characteristics included median age 35 (IQR: 26 to 41), 10/12 were white and 11/12 were using daily PrEP. Median number of partners in previous 3 months was 19 (IQR: 14 to 34) with receptive sex without condoms reported with a median 8 partners (IQR: 3 to 22). Although 9/12 (95%) reported chemsex (use of crystal meth, mephedrone or GHB), information was not included about whether this included shared injections.

Phylogenetic analyses were compared to HIV positive cohorts and other risk groups in the Netherlands, and showed a high degree of clustering (four large clusters, all HCV 1a) between HIV positive and HIV negative gay men, suggesting a shared transmission network.

The study emphasised the importance of routine HCV testing and prompt HCV treatment.

COMMENT

Unlike the UK, the Netherlands health service includes not only access to effective DAA treatment but repeated access if reinfection occurs.

This is the right public health intervention to HCV prevention if HCV is to be eradicated as an STI for gay men. This is especially true given the difficulty in identifying the exact transmission route, still most likely involving blood-to-blood contact.

Reference

Hoornenborg E et al. High incidence of hepatitis C virus (re-)infections among PrEP users in the Netherlands: Implications for prevention, monitoring and treatment. AIDS 2018, 23-27 July 2018, Amsterdam. Poster TUPEB038.

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AIDS 2018: CURE RESEARCH

FDA-approved compounds that might selectively reverse HIV latency

Simon Collins, HIV i-Base

A late breaker poster from researchers at UCSF in collaboration with Merck reported optimistic news that a selection of already FDA-approved small molecule compounds selectively activate latently infected cells in vitro.

The level of activity from some compounds was greater than romidepsin (the HDAC-inhibitor that has been previously used in human studies). The new compounds include sorafenib, sunitinib, axitinib, cabozantinib, regorafenib and carfilzomib that target new pathways (inhibiting VEGF, RAF-1, B-RAF and the proteosome). Importantly, they did not show global activation of uninfected cells, also shown in vitro in CD4 cells from HIV positive people on supressed ART.

Previously studied compounds have generated broad CD4 cell activation, but at too low a level to be able to show clinical impact in reducing the viral reservoir.

Unfortunately only limited information is available from the study abstract and the poster is not yet available to download from the conference website.

Ref: Munoz-Arias I et al. FDA-approved chemotherapeutic drugs that inhibit VEGF, RAF-1, B-RAF and the proteosome reverse HIV latency without global T cell activation. **AIDS 2018, 23-27 July 2018, Amsterdam.** Late-breaker poster LBPEA006.

http://programme.aids2018.org/Abstract/Abstract/13445

Lack of impact on viral reservoir with α4β7 monoclonal antibody vedolizumab: macaque results not matched in humans

Simon Collins, HIV i-Base

In 2016, impressive results generated headline news in Science after vedolizumab in a monkey study generated SIV remission without ART in approximately half the animals. [1]

Unfortunately, an extension to this study trying to duplicate the first results (using12 active and 10 controls) was presented at AIDS 2018, but found no differences in the active vs control groups. [2]

Also unfortunately, the first results using vedolizumab (already FDA-approved as a treatment for Crohn's disease) in a human study also failed to see any effect.

Although two studies included results that suggest vedolizumab might be safe in HIV positive people [3, 4], there was no impact on time to viral rebound after stopping ART in 18 participants, even after various post hoc analysis (using historical controls to overcome the lack of a control arm in the open-label study). There was considerable variability in the range of results however that did include two cases without viral rebound. [4]

Nevertheless, presenting these results, NIAID director Anthony Fauci "remained optimistic" about passive transfer of combinations of monoclonal antibodies during acute HIV infection.

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   http://programme.aids2018.org/Programme/Session/37 (slides)
   https://www.youtube.com/watch?v=KK05hDfLKKE (webcast)

Janssen HIV vaccine: update from APPROACH and largescale efficacy study

Simon Collins, HIV i-Base

As an HIV vaccine is likely to be a critical component of an HIV cure, ongoing results presented by Frank Tomaka and colleagues from Janssen were encouraging for showing improved immune responses to a promising new preventative HIV vaccine. [1]

These were from the phase 2 APPROACH study first presented last year and published in the Lancet in the weeks before AIDS 2018. [2]

This analysis included longer follow-up. All participants generated immune responses that were higher than levels that protected monkeys in animal studies and that were maintained for more than a year and five-year follow-up is planned.

Based on these results a large efficacy study called Imbokodo is already ongoing. Although this new study was referred to several times as phase 3 at the conference, the trial listing is as phase 2. [3, 4]

A second related presentation also suggested that a shorter 24-week vaccine schedule might be just as effective as the 48 week schedule currently used in the Imbokodo study. [5]

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   http://programme.aids2018.org/Abstract/Abstract/11441 (abstract and slides)

AIDS 2018: DIAGNOSTICS

Viral load testing in Latin America and the Caribbean

Simon Collins, HIV i-Base

Information about routine access to viral load testing in 31 countries in Latin America and the Caribbean (LAC) was presented in a poster by researchers from the Pan-American Health Organisation.

Results were compiled from official surveys (UNAIDS/WHO/UNICEF) at the end of 2016 to assess existing gaps in viral load testing policies, capacity and coverage.

All countries had access to viral load testing but guidelines varied for recommended testing frequency: two tests per person per year in 61% countries (19/31), annually in 32% (10/31) and more frequently in Costa Rica and the Bahamas.

The poster compared the number of viral load tests that were performed over a two-year period with the expected number needed, based on the numbers of people who were positive and the national policy for testing.

Of 22/31 countries with this data, 7/22 exceeded 90% of estimated need (range 92% to 170%) with 11 countries reporting 51% to 87% of expected use, and four countries <50% (range (16% to 48%).

A second analysis based on a standardised policy of two viral load tests a year produced similar results, with 6 countries at >90% use, 12 countries with between 50% to 90% use, and 7 countries at <50% use.

In this analysis, lowest use was reported for Haiti (16%), Cuba (21%) and highest use for Brazil (99%) and Bahamas (110%).

Further results by country are reported in the abstract and poster.

Reference

Leal A et al. Are all people on antiretroviral treatment having their HIV viral load monitored? Gaps analysis in Latin America and the Caribbean. AIDS 2018, 23-27 July 2018, Amsterdam. Poster TUPEB044.
http://programme.aids2018.org/Abstract/Abstract/12601

Access to viral load testing increased from 14% to 61% over two years in Côte d'Ivoire

Simon Collins, HIV i-Base

An interesting poster presented results on the recent scale up of access to viral load testing in rural and urban clinics in Côte d'Ivoire from 2015 to 2017.

Before 2015, viral load was available to less than 10% of HIV positive people, and was restricted to clinics in the capital Abijan and the scale-up programme used internet-enabled quantitative lab-in-the-box technology. Viral load is recommended every 6 months during the first year of ART and annually thereafter.

Between October 2015 and August 2017, almost 222,000 people received ART, with 85% 12-month retention rate. Access to at least one viral load test increased from 14% to 61%, reaching almost 135,000 people. This included 41% of HIV positive people attending clinics outside the capital. Over the same period, the number of laboratories increased from 6 to 15.

Among those with access, 74% were women and 6% were children (<14 years), with 77% (95%CI: 55 to 82) overall testing <1000 copies/mL (similar rates for men and women). Viral suppression was lowest in children and adolescents (55%) and was 67% in young adults' (20 to 24 years) and 79% in people >25 years.

This study showed progress in increasing access to viral

load testing in a low-income country and that access can be effectively broadened. This programme emphasised the importance of a strong sample transportation system and minimising reagent stock-out.

Reference

Adje-Toure C et al. Increased access to HIV viral load testing among ART patients in Côte d'Ivoire (2015 to 2017). AIDS 2018, 23-27 July 2018, Amsterdam. Poster TUPEB043.

http://programme.aids2018.org/Abstract/Abstract/10852

Resolving a diagnosis for people with persistently indeterminate HIV test results

Simon Collins, HIV i-Base

A poster from the UK outlined an important practical way to resolve HIV diagnoses for the small minority of people who persistently have indeterminate results.

This study was presented by Colin Brown from Public Health England, with colleagues from the Royal Free and Imperial College and included 14 cases when HIV tests showed low-level or indeterminate antibodies and negative results to standard HIV RNA/DNA testing.

All participants provided a larger blood sample (60 mL) that was divided equally between a clinical, academic, and public health laboratory, and immediately processed.

Despite all samples testing RNA negative using a 20 copy/mL cut-off, molecular testing using a single copy viral load test amplified HIV RNA in 8/14 cases and was DNA positive in another 2/14. Western blot results (not routinely used in the UK) showed 11/14 positive to p24 and 12/14 positive to gp160. Use of CD4, CD8 and ratio were not helpful in showing any unexpected results.

These more sensitive tests were able to confirm 11/14 diagnoses, refute 1 diagnosis, with only 2/14 left unresolved.

One of these individuals on PEP converted to ART on diagnosis and one developed high-level viral load.

This study confirmed that western blot is an essential test for indeterminate results and commented that such cases might become more common in the context of wider use of PrEP, where the decision to change to early ART might be particularly important.

Reference

Brown C et al. Adapting HIV testing algorithms and clinical advice for people with persistently indeterminate test results - a novel national referral clinical service. AIDS 2018, 23-27 July 2018, Amsterdam. Poster TUPEB038.

http://programme.aids2018.org/Abstract/Abstract/9844

CONFERENCE REPORTS

10th International Workshop on HIV Paediatrics

20–21 July 2018, Amsterdam

The 10th International Workshop on HIV Paediatrics was held 20–21 July 2018 in Amsterdam, just before the AIDS 2018 conference.

The paediatrics workshop is the only HIV meeting devoted to research in prevention and treatment for infants, children and adolescents. Since 2009, this workshop has preceded the IAS conference and dual submissions to both meetings are permitted.

This year's meeting included: pharmacokinetic and early safety and efficacy data for dolutegravir in children aged four weeks to six years; the first public presentation from the Tsepamo study of a potential safety signal with dolutegravir from conception; first data from the ODYSSEY trial; data on tenofovir alafenamide in the bictegravir-based fixed dose combination for six to twelve year olds; and much more.

The abstracts as well as slides of the presentations and webcasts are posted online when consent has been provided.

http://www.infectiousdiseasesonline.com

Conference website:

http://www.virology-education.com/event/upcoming/10th-workshop-hiv-pediatrics

HTB reports from this workshop are:

- Dolutegravir dispersible tablets for infants and young children: early PK, safety and efficacy

Dolutegravir dispersible tablets for infants and young children: early PK, safety and efficacy

Polly Clayden, HIV i-Base

Once daily dolutegravir dispersible tablets achieved exposure within target range for most children aged four weeks to less than six years, participating in IMPAACT P1093. But due to moderate inter-patient variability, higher dosing is likely to be needed for children two to less than six years of age.

These results were presented at the 10th International Workshop on HIV Paediatrics.

IMPAACT P1093 is an ongoing phase 1/2 open label pharmacokinetic (PK), safety, and dose-finding study of dolutegravir (DTG).

Film coated tablets are approved for older children (aged 6 and above) in the US and EU. A 5 mg DTG dispersible tablet (DTG-DT) paediatric formulation is being evaluated for younger children.

Theodore Ruel presented intensive PK and 4-week safety (primary outcomes) as well as tolerability and efficacy data for DTG-DT tested infants and children ages 4 weeks to <6 years.

Dosing in P1093 is by age cohort. Thirty-two children were enrolled to achieve 30 with evaluable data, 10 in each cohort: 4 weeks to <6 months; 6 months to <2 years and 2 years to <6 years.

Of these children, 43% were female; at baseline 90% had CD4 percent >14 and 53% had viral load >50, 000 cells/mL. Over 80% were from Africa (Botswana, South Africa, Tanzania and Zimbabwe) and the remainder were enrolled from Brazil, Thailand and the US.

Participants received DTG-DT as monotherapy at enrollment, or added to stable-failing or empiric initial background regimens and were dosed using weight-band tables. See table 1.

Table 1: Initial DTG-DT once daily dosing table

Weight band (kg)	Dose (mg)	Dose (mg/kg) for weight range	
		Lower weight	Upper weight
3 to <6	5	1.67	0.83
6 to <10	10	1.67	1.00
10 to <14	15	1.50	1.07
14 to <20	15	1.79	1.25
20 to <25	20	1.50	1.20

Intensive 24-hour PK sampling was completed between days 5–10, after which background regimens were optimised based on genotypes. Fifteen of the participants received AZT/3TC, four ABC/3TC, and five received LPV/r with either one or two NRTIs, as background regimens.

From adult data, targets (range) for geometric mean (GM) exposures were AUC24h 46 (37–86) mgxh/L and C24h 750 (500–2260) ng/mL.

Median (range) age (in years) and doses (in mg/kg), followed by the GM (arithmetic CV%) AUC24h (mgxh/L) and C24h (ng/mL) were as follows: 2 to <6 years 4.0 (2.1–5.9), 1.1 (0.8–1.6), 40 (36%) and 461 (59%); 6 months to <2 years 1.2 (0.9–1.9), 1.2 (1.0–1.4), 51 (38%) and 711 (60%); and 4 weeks to 6 months 0.34 (0.28–0.39), 1.2 (0.9–1.7), 61 (44%) and 1207 (55%).

DTG exposures showed moderate inter-patient PK variability: 8/10 in each of the two younger cohorts achieved C24h above the lower acceptable limit (>500 ng/mL), but only 4/10 achieved the lower limit in the 2 to <6 years cohort.

DTG-DT was well-tolerated, with no grade 3 or 4 adverse events or discontinuations attributed to study drug. At 4 weeks, 24/30 (80%) subjects had viral load <400 copies/mL or a >2 log decrease.

C O M M E N T

Higher doses of DTG are now being evaluated for the 2 to <6 years age group. And the next protocol version of P1093 allows for additional enrollments to ensure data to support WHO weight band and age-based dosing.

Reference

Ruel T. Pharmacokinetic and 4-week safety/efficacy of dolutegravir (S/GSK1349572) dispersible tablets in HIV-infected children aged 4 weeks to <6 years: results from IMPAACT P1093. 10th International Workshop on HIV Paediatrics. 20 –21 July 2018. Oral abstract 2. Link to slides:

http://regist2.virology-education.com/presentations/2018/10PED/16_ruel.pdf (PDF)

ANTIRETROVIRALS

Top-line phase 3 results released for cabotegravir/rilpivirine long-acting injections

Simon Collins, HIV i-Base

On 15 August 2018, top-line results from the phase 3 ATLAS study reported that monthly injections with the dual long-acting formulation cabotegravir/rilpivirine were non-inferior as a switch option compared to remaining on triple-drug ART. [1]

The Antiretroviral Therapy as Long Acting Suppression (ATLAS) study randomised 570 HIV positive adults who had been virally suppressed for more than six months on their first or second HIV combination. [2]

The top-line results are based on the primary endpoint of viral suppression at week-48. However, as the recent FDA requirement for tigher boundaries for the confidence intervals is likely to apply to both ATLAS and the similar phase 3 FLAIR study, these early results are likely to be very encouraging.

Additional details were not included in the press statement other than the full study results will be presented at an upcoming medical conference.

COMMENT

The early press release of results is a governance requirement for all companies with publicly traded stock.

However, meeting the primary endpoint of non-inferiority is an important marker that injectable ART is one step closer.

Even though oral ART is extremely effective with limited side effects, there has always been considerable interest in alternatives to taking pills. The development of injectable ART is therefore an option that many people have been waiting for.

A multi-country named-patient programme is already open and this includes expanded access in the UK. [3]

This is for people who are in need of new drugs to construct an effective ART combination and who may require the use of injectable drugs.

References

1. ViiV press release. ViiV Healthcare reports positive 48-week results for first pivotal, phase III study for novel, long-acting, injectable HIV-treatment regimen. (15 August 2018) https://www.viivhealthcare.com/media/press-releases/2018/viiv-healthcare-reports-positive-48-week-results-for-first-pivotal-phase-iii-study-for-novel-long-acting-injectable-hiv-treatment-regimen.aspx
2. clinicaltrials.gov. Study evaluating the efficacy, safety, and tolerability of switching to long-acting cabotegravir plus long-acting rilpivirine from current antiretroviral regimen in virologically suppressed HIV-1-infected adults. https://clinicaltrials.gov/ct2/show/NCT02951052
3. clinicaltrials.gov. GSK1265744 (cabotegravir, CAB) for named patient/ compassionate use in HIV. https://clinicaltrials.gov/ct2/show/NCT03462810

Interactions between oral anticoagulants and Genvoya, Stribild and cobicistat: FDA label updates

Simon Collins, HIV i-Base

On 15 August 2018, the FDA listserv announced label changes to several HIV combinations based on drug interactions with oral anticoagulants.

A summary of the changes is bulleted below, but please check updated package inserts for full details.

Genvoya and Stribild

Genvoya and Stribild are both expected to increase the exposures of apixaban, rivaroxaban, betrixaban, dabigatran and edoxaban. The specific recommendations are as follows:

- Apixaban: Due to potentially increased bleeding risk, dosing recommendations for coadministration with Genvoya or Stribild depends on the apixaban dose. Refer to apixaban dosing instructions for coadministration with strong CYP3A and P-gp inhibitors in apixaban prescribing information.
- Rivaroxaban: Coadministration of rivaroxaban with Genvoya or Stribild is not recommended because it may lead to an increased bleeding risk.
- Betrixaban, dabigatran, edoxaban: Due to potentially increased bleeding risk, dosing recommendation for coadministration of betrixaban, dabigatran or edoxaban with a P-gp inhibitor such as Genvoya or Stribild depends on the direct oral anticoagulant indication and renal function. Refer to the direct oral anticoagulant dosing instructions for coadministration with P-gp inhibitors in the direct oral anticoagulant prescribing information.

Tybost coadministered with atazanavir or darunavir:

- Apixaban: Due to potentially increased bleeding risk, dosing recommendations for coadministration of apixaban with Tybost depends on the apixaban dose. Refer to apixaban dosing instructions for coadministration with strong CYP3A and P-gp inhibitors in apixaban prescribing information.
- Rivaroxaban: Coadministration of rivaroxaban with Tybost is not recommended because it may lead to an increased bleeding risk.

Tybost coadministered with atazanavir:

- Betrixaban, dabigatran and edoxaban: Due to potentially increased bleeding risk, dosing recommendations for coadministration of betrixaban, dabigatran, or edoxaban with a P-gp inhibitor such as Tybost coadministered with atazanavir depends on DOAC indication and renal function. Refer to DOAC dosing instructions for coadministration with P-gp inhibitors in DOAC prescribing information.

Tybost coadministered with darunavir:

- Betrixaban, dabigatran and edoxaban: No dose adjustment.

Reference

FDA list serve (13 August 2018).

OTHER NEWS

More than ten people a day died from drug-related deaths in England and Wales last year: increasing rates from cocaine and fentanyl, rates from heroin and morphine still remain high

Simon Collins, HIV i-Base

On 6 August 2018, the latest annual data was published relating to drug-related deaths in England and Wales. This report from the Office for National Statistics (ONS) is predominantly a register of fatalities from overdose or poisoning from legal and non-legal drugs.

Overall, 3756 cases were registered in 2017, compared to 3744 in 2016 and 3674 in 2015.

More than half of these deaths (1985/3756) were related to opiates - including heroin/morphine (1164), methadone (367), tramadol (385), fentanyl and related analogues (106) and cannabis (29)

Cocaine-related deaths increased from 371 in 2016 to 432 in 2018. Antidepressants were listed as the cause of death in 484 cases.

New psychoactive compounds were listed for 61 cases, included 17 people for GHB and 24 people for synthetic cannabinoids.

A press statement from Release, a campaigning organisation for drug reform, highlighted the continued increase linked to cocaine and fentanyl, increasing by 16% and 80% respectively, both the highest over the 25 years that data has been collected. They highlight the figures as a national crisis that requires a coordinated, national public health response. [2]

Release call for changes in government policy to decriminalise drug possession, to allow life-saving drug consumption rooms, scaled up access to naloxone and to reinstate budget cuts to essential drug-related services. England and Wales have one of the highest rates of drug-related deaths in the EU. It is more than 17 times higher than Portugal, which decriminalised all personal drug possession in 2001.

References

1. Deaths related to drug poisoning in England and Wales: 2017 registrations. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2017registrations
2. Release press release. Drug-related deaths in England & Wales reach highest figure on record, Government policy directly contributing to public health crisis: Deaths relating to cocaine and fentanyl highest on record. (06 August 2018). https://www.release.org.uk/media-enquiries

ON THE WEB

We learn, we think, we change: Martin Fisher Foundation and Stiggy launch campaign to end stigma

Simon Collins, HIV i-Base

The Martin Fisher Foundation (MFF) together with Stiggy the stigmasaurus, has produced a new set of videos about making HIV Stigma History.

These include up-to-date information on the impact HIV treatment has on transmission and on the effectiveness of treatment in general.

One video looks at HIV disclosure at work to tackle common prejudice.

One involves disclosing HIV to your family and another includes interviews where HIV positive people discuss the impact that stigma has on our lives.

A related social media campaign is using the hashtag:

#makingHIVstigmahistory

Follow Stiggy on social media (FaceBook, Intsagram etc) on:

@stigma_saur

To view these videos and for more details of the campaign please visit the MFF website.

https://www.themartinfisherfoundation.org/makinghivstigmahistory

The website also includes information on other MFF projects, including the new HIV test vending machines and committing Brighton and Hove to be the UK's first fast-track city (to meet the UNAIDS 90:90:90 goal by 2020).

FUTURE MEETINGS

Conference listing 2018/19

The following listing covers some of the most important upcoming HIV-related meetings and workshops.

International Workshop on HIV & Ageing

13 –14 September 2018, New York, USA.

www.virology-education.com

Australasian HIV&AIDS Conference 2018

24 – 26 September 2018, Sidney

www.hivaidsconference.com.au

BHIVA Autumn Conference

4 – 5 October 2018

www.bhiva.org

20th International Workshop on Comorbidities and Adverse Drug Reactions in HIV

13 – 14 October 2018, New York

https://www.intmedpress.com/comorbidities

HIV Research for Prevention (HIVR4P 2018)

21 – 25 October 2018

www.hivr4p.org

HIV Glasgow 2018

28 – 31 October 2018, Glasgow

www.hivglasgow.org

26th Conference on Retroviruses and Opportunistic Infections (CROI 2019)

4 – 7 March 2018, Seattle

www.croiconference.org

25th Annual BHIVA Conference

2 – 5 April 2019, Bournemouth

www.bhiva.org

10th IAS Conference on HIV Science

21-24 July 2019, Mexico City

http://www.ias2019.org

17th European AIDS Conference

6 – 9 November 2019 Basel, Switzerland

https://eacs-conference2019.com

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

All i-Base publications are available online, including editions of the treatment guides.

http://www.i-Base.info

The site gives details about services including the UK Community Advisory Board (UK-CAB), our phone service and Q&A service, access to our archives and an extensive range of translated resources and links.

Publications and regular subscriptions can be ordered online.

The Q&A web pages enable people to ask questions about their own treatment:

http://www.i-base.info/qa

i-Base treatment guides

i-Base produces six booklets that comprehensively cover important aspects of treatment. Each guide is written in clear non-technical language. All guides are free to order individually or in bulk for use in clinics and are available online in web-page and PDF format.

http://www.i-base.info/guides

- Introduction to ART (May 2018)
- HIV & quality of life: side effects & long-term health (Sept 2016)
- Guide to PrEP in the UK (November 2016)
- HIV testing and risks of sexual transmission (June 2016)
- Guide to changing treatment and drug resistance (Dec 2017)
- Guide to HIV, pregnancy & women's health (December 2015)

New pocket guides

A new series of pocket-size concertina folding leaflets that is designed to be a very simple and direct introduction to HIV treatment.

The first five pocket leaflets are: Introduction to ART, HIV and pregnancy, ART and quality of life, UK guide to PrEP and HCV/HIV coinfection.

We hope these are especially useful as low literacy resources.

The leaflets use simple statements and quotes about ART, with short URL links to web pages that have additional information in a similar easy format.

Order publications and subscribe online

All publications can be ordered online for individual or bulk copies. All publications are free. Unfortunately bulk orders are only available free in the UK.

http://i-base.info/order

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All publications are free, including bulk orders, because any charge would limit access to this information to some of the people who most need it.

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Pocket ART	**quantity** _____	**Pocket pregnancy**	**quantity** _____
Pocket side effects	**quantity** _____	**PrEP for women**	**quantity** _____

- **Booklets about HIV treatment**

ART in pictures: HIV treatment explained *(August 2018): 32-page A4 booklet* **quantity** _____

Guide to hepatitis C coinfection *(April 2017): 52-page A5 booklet* **quantity** _____

UK Guide To PrEP *(November 2016): 24-page A5 booklet* **quantity** _____

Introduction to ART *(May 2018): 48-page A5 booklet* **quantity** _____

HIV and quality of life: guide to side effects and long-term health *(Sept 2016): 96-page A5* **quantity** _____

Guide to HIV testing and risks of sexual transmission *(July 2016): 52-page A5 booklet* **quantity** _____

Guide to HIV, pregnancy and women's health *(November 2015): 52-page A5 booklet* **quantity** _____

Guide to changing treatment: what if viral load rebounds *(Jan 2018): 24-page A5 booklet* **quantity** _____

- **Other resources**

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