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EDITORIAL

The first HTB in 2015 includes a diverse selection of HIV related news and research reviews.

We report from the Five Nations conference on HIV and Hepatitis held in London, which included a statement on the importance of increasing access to HCV treatment. Access was a recurring theme – as, even in Europe, the new drugs seem likely to only reach a small proportion of those who could benefit from using them.

From the 45th Conference on Lung Health, held in Barcelona we report studies about both new and existing treatment for TB and MDR-TB in HIV positive adults and children. Notably, an early safety concern with bedaquiline is not being reported from compassionate access programmes.

Again on access, NHS England has decided that dolutegravir can now be used. London guidelines - currently only available to download from the i-Base website - also agree. This must mean the price is comparable to other options, though in London, separate abacavir/3TC plus dolutegravir is recommended for financial reasons, rather than the 3-in-1 single pill formulation of Triumeq.

Two studies with importance for global health, include one report that efavirenz CSF levels are similar with 400 mg and 600 mg doses and another, less surprising, that triple therapy is more effective than a single drug regimen to prevent mother to child transmission at 2 weeks.

We include news that India has rejected Gilead's patent application for sofosbuvir. This is a considerable victory for all countries dependent on modern generic medicines. Gilead is challenging this decision and our commentary includes more detail. Also, news on why patients in non-EU Morocco are concerned about EU patent laws.

Towards the end of last year, one of the most widely reported study in mainstream media on World AIDS Day, was that HIV may be becoming weaker. Richard Jefferys was less convinced, and we include his somewhat cooler analysis that explains why.

Other basic science reports include Gareth Hardy's review of the data on the role of vorinostat in cure research, further concerns about CMV coinfection and the impact of smoking on life expectancy of HIV positive people.

In the next issue of HTB we will be reporting from CROI which is being held at the end of February. Our reports are likely to be led with results from the PROUD and IPERGAY PrEP studies. It is therefore notable that the early results from these studies are already generating demand for PrEP in the UK, and we reprint a community statement that had over 1200 signatures as we went to press, together with news that ACT-UP London held a protest in supporting early access.

Access to PrEP is also one of three proposed strategies proposed for dramatically reducing HIV incidence in New York State by 2020. The policy, reported here with links to the Task Force that developed it, not only had high-level political engagement, but also set numerical targets - ie to reduce annual incidence from 3000 to 750 within five years,

Meanwhile, plans in the UK to reduce HIV prevention funding for 2015, seem to have been averted, at least in the short-term. This is thanks to an NAT-initiated community response, but it highlights how important community engagement will be throughout 2015.

CONFERENCE REPORTS

Five Nations Conference on HIV and Hepatitis

8-9 December 2014, London

Introduction

A new joint European conference on HIV hepatitis coinfection was held from 8-9 December 2014 in London and attended by approximately 400 delegates.

Building on the annual meeting organised by BHIVA in previous years, six other professional organisations from France, Germany, Italy, Spain and the UK collaborated to support and expand the meeting to a European one.

The programme, abstract and webcasts are posted online for open access.

This includes presentations from the excellent pre-conference clinical and nurse's courses.

<http://www.bhiva.org>

Reports from this meeting in this issue of HTB are:

- Summary of the pre-conference clinical course
- Hepatitis C drug access: Europe is the new Africa

Summary of the pre-conference clinical course

Simon Collins, HIV i-Base

A pre-conference clinical course on the morning of the first day of the conference included five expert overviews.

The first presentation was from Carlo-Federico Perno from the University of Rome on the history and virology of HCV. [1]

This highlighted key differences with HCV compared to either HIV or HBV. Because HCV replicates without integration into human DNA, unlike HIV or HBV, HCV treatment can cure HCV infected hepatocytes, allowing the cells to actively continue reversing liver damage for several weeks. Before treatment, a single cell might be supporting up to 40 cycles of HCV replication, running simultaneously at different stages in the viral lifecycle. In advanced liver disease, the restricted blood flow in the liver, resulting from cirrhosis, is a rate-limiting step by preventing optimal intracellular drug levels. The lecture also reviewed HCV drug resistance, concluding that baseline genotypic testing is not only important but cost effective.

In the second talk, Karine Lacombe from Hôpital Saint-Antoine, Paris, gave an overview of tests and algorithms for diagnosis and management. [2]

Sanjay Bhagani, from the Royal Free Hospital, London, reviewed the data supporting increased risk of serious complications for patients with coinfection together with the importance of early HCV treatment (contrary to the indications for delayed access to new direct acting antiviral [DAA] drugs). [3]

In the fourth talk, Patrick Ingiliz from Medical Centre for Infectious Diseases, Berlin, reviewed the data on new HCV drugs from the perspective of limited access to DAAs. [4]

Although current European guidelines have important differences across countries, none of these documents will last longer than 6-12 months because of the rapid advances in drug development. The talk highlighted rates of 25% HCV reinfection in the NEAT centres. In an overview of latest treatment, including complex cases and drug interactions, Dr Ingiliz concluded that future treatment uptake will mainly be driven by cost: "we will treat who the payers are willing to pay for".

In the final talk, Graham Foster from the Queen Mary University of London presented an overview of the management of end-stage liver disease and its complications, again from the perspective of limited access to new treatment. [5]

In the UK, 10,000 people already have HCV-related cirrhosis, with approximately 4-5% people each year likely to progress to decompensated disease, and 4-5% to hepatocellular carcinoma (HCC), with some overlap between these groups. By 2020, without new treatment, more than 11,500 people in the UK will have cirrhosis and 4,200 will have progressed to decompensated disease or HCC. Old drugs are hard to use, have a high failure rate, and a high risk of serious toxicity. This demands the use of new drugs.

Early UK data was presented from the first 250/700 patients with decompensated cirrhosis who have been treated with sofosbuvir plus either ledipasvir or daclatasvir with ribavirin, and HCV relapse was only seen in seven cases.

References

All references relate to the pre-conference clinical course for the Five Nations Conference on HIV and Hepatitis 8-9 December 2014, London. Webcasts and PDF slides from all sessions are online.

<http://www.bhiva.org/Presentations141208.aspx>

1. Perno CF. The history and basics of HCV virology.
2. Lacombe K. Clinical evaluation of HCV-induced liver disease.
3. Bhagani S. The impact of HIV on hepatitis C and vice versa.
4. Ingiliz P. Treatment of hepatitis C: who, when and how.
5. Foster G. End-stage liver disease and its complications.

Hepatitis C drug access: Europe is the new Africa

Simon Collins, HIV i-Base

Leading doctors, researchers and community activists involved in the Five Nations meeting collaborated on a joint public statement that called for "governments, the pharmaceutical industry and the medical profession to co-operate to make the latest and most effective hepatitis C drugs affordable and accessible to all patients". [1]

The statement was important, as treatment access and cost were repeated themes throughout the conference. As the meeting progressed, it became increasingly clear that the remarkably high cure rates being reported with the newest hepatitis C drugs were only likely to be used by a tiny percentage of people who needed them.

The current arrival of new HCV treatment is often historically compared to the availability of ART to treat HIV in the mid 1990s from the standpoint of new drugs and the dramatic impact they had on mortality and morbidity. But just as HIV drug pricing limited access to people in rich countries, without concerted public health campaigns, the new HCV drugs will similarly be denied to most people in need. The surprise for many is that this disparity is occurring within rich European countries. For many people, Europe is the new Africa. Many of the European activists speaking in the programme reported little prospect of access to treatment, despite long-term HIV/HCV coinfection and progression to cirrhosis.

As EATG activist Diego Garcia Morcillo explained in a plenary session on access: "People are dying, it is that simple. We have forgotten the lessons we learned from HIV. In South Africa, pharmaceutical companies blocked access to generic medicines. Now it is happening in Europe." [2]

This session highlighted disparities in access in different European countries - with Germany and France having broader access to new treatments, but with Spain, Italy and the UK planning to limit access to those with the most advanced disease. The exorbitant prices set for these drugs is holding public health systems to ransom. Individual patients who are diagnosed and within care will have to let their liver function progressively decline until this is judged sufficiently serious to warrant tolerable treatment with best standard of care.

Dr Edmund Wilkins, one of the senior HIV and HCV consultants involved in the BHIVA coinfection guidelines noted in the Janssen satellite meeting before the first plenary: "For the next year we are still going to be using interferon-based treatment, and interferon is not a drug that anyone wants to be taking". [3]

References

1. Conference statement. European experts call for reduction in treatment costs to 'eliminate Hep C within our lifetimes. (08 December, 2104). <http://www.bhiva.org/european-experts-call-to-eliminate-Hep-C.aspx>
2. Diego Garcia Morcillo. Plenary Session 6 HIV/hepatitis in Europe: who, when and where. Five Nations Conference on HIV and Hepatitis 8-9 December 2014, London. <http://www.bhiva.org/141209DiegoGarciaMorcillo.aspx>
3. Wilkins E. HIV and hepatitis C: the patient's journey through a clinical setting. Five Nations Conference on HIV and Hepatitis 8-9 December 2014, London. Session not available online.

CONFERENCE REPORTS

45th Union World Conference on Lung Health

28 October – 1 November 2014, Barcelona, Spain.

Introduction

The annual Union World Conference on Lung Health took place in Barcelona late October last year.

The final programme and PDF file of the abstracts are available from the conference website:

<http://barcelona.worldlunghealth.org/programme/final-programme>

<http://barcelona.worldlunghealth.org/programme/abstracts>

Although some of the slide presentations are online the website is not easy to navigate:

<http://slideonline.eu/recordings/2014/14union>

Reports from this meeting in this issue of HTB are:

- Good outcomes within the National Bedaquiline Clinical Access programme in South Africa
- Pharmacokinetics and safety of moxifloxacin in children
- TB in the ARROW trial of children on ART
- Problems giving current second line TB drugs to children

Good outcomes within the National Bedaquiline Clinical Access programme in South Africa

Polly Clayden, HIV i-Base

The South African Bedaquiline Clinical Access Programme showed good interim outcomes in people with drug resistant tuberculosis (DR-TB), according to data presented at the 45th Union Conference on Lung Health.

Bedaquiline is a diarylquinoline compound with a novel anti-tuberculosis mechanism of action that inhibits mycobacterial ATP synthase. Janssen Therapeutics manufactures this drug. The FDA approved bedaquiline for the treatment of multi-drug resistant (MDR) TB in December 2012. It was the first new anti-TB drug to be approved by the agency in over forty years.

In December 2012 the South African Medicine Control Council (MCC) approved a national programme to treat selected DR-TB patients with bedaquiline, which began in March 2013.

Dr Ndjeka from the National Department of Health presented results on behalf of colleagues from the programme.

He began the presentation by describing the TB burden in South Africa. He noted that the number of people with TB initiated on treatment was decreasing: between 2009 and 2013 this went from 406,082 to 332,170, with an 80.9% success rate in 2012. But numbers with MDR-TB initiated on treatment doubled between 2010 and 2013: from 5,313 to 10,719, with a 45% success rate. For extensively drug resistant (XDR) TB treatment success is only between 15% and 20%.

Laboratory-confirmed pre-XDR and XDR TB patients at five approved South African sites received bedaquiline according to predefined selection criteria: ≥ 18 years of age, susceptible to at least three anti-TB drugs with which to construct the background regimen, negative pregnancy test and using contraception. Pregnant or breastfeeding women and patients with serum creatinine grade ≥ 1 , lipase grade 2, ALT or AST grade 2 or total bilirubin grade ≥ 1 were excluded.

The cases were presented to a clinical advisory committee, after which the originator company approved bedaquiline with an optimised background regimen of at least three selected second line anti-TB drugs and the MCC approved the prescription on a named-patient basis.

400 mg bedaquiline was given once daily for two weeks followed by 200 mg three times a week for 22 weeks plus optimised background regimen. The optimised background regimen continued beyond the 22 weeks.

At base line the 91 participants in the programme, included in the interim analysis, were a median age of 34.1 years (IQR 25.7 – 40.9), 56 (60.5%) were male and 55 (60.5%) were coinfecting with HIV. The HIV positive group had a median CD4 count of 249 cells mm³ (IQR 134 – 356), 19 (34.5%) received lopinavir/ritonavir-based ART regimens and 36 (65.5%) nevirapine-based.

TB drug resistance patterns were described as: XDR in 33 (36.3%) participants, pre-XDR (fluoroquinolone) in 41 (45.1%) and pre-XDR (injectable) in 17 (18.1%). Optimised background regimens included: clofazimine for 68 (74.5%), linezolid for 64 (70%) and levofloxacin for 76 (83.5%).

At the time of analysis, 60 participants had > 24 weeks of follow up, 2 did not complete bedaquiline (1 died, 1 lost to follow up). Of 58 that completed 24 weeks of bedaquiline, 2 died, 1 transferred and 1 was lost to follow up. Of the remaining 54 on continuation treatment, 15 were culture negative at start, 33 culture-converted and 6 were still culture positive. All the 31 participants with < 25 weeks of follow up since treatment start were still on treatment. Of this group, 6 were culture negative at start, 10 culture- converted, and 15 participants had not yet received culture results.

One participant developed atrial fibrillation on bedaquiline and was withdrawn from treatment. At start of bedaquiline, median QTcF was 408ms (IQR 390-426); there was a median increase of 8 ms (IQR -12 to 31 at 2 months; 14 had increases of > 40 ms and 2 had QTc $>$ ms (bedaquiline was temporarily withdrawn in 1 and the other resolved in 24 hours).

Fifteen participants experienced serious adverse events. The general pattern and frequency were considered to be in line with the known safety profile of bedaquiline. There were 3 deaths of which none were related to bedaquiline; 3 QT prolongation probably or possibly related (all resolved); and 3 psychosis/mood disorder/delusion, none related to bedaquiline (all 3 were receiving terizidone, prodrug of cycloserine known to cause mood disorder).

The programme has since been extended to include 12 sites in South Africa.

In October 2014 the MCC approved bedaquiline and it will be used within the national TB programme under strict control.

C O M M E N T

Bedaquiline added to a background regimen was associated with earlier culture conversion and higher cure rates in its registrational trials, but there were unexplained excess deaths in the bedaquiline arms of these studies.

When the FDA approved bedaquiline for treatment of MDR-TB when an effective treatment regimen cannot otherwise be given this included a black box warning about excess deaths and a requirement to complete a phase III trial.

As a result, many programmes, including in South African, were right to approach the drug with caution, and it is reassuring that further safety events were not reported.

The French compassionate use programme has been similarly reassuring. [2] At 6 months, 28/29 (97%) participants with culture-positive TB achieved culture conversion in a median of 85 days (range 8–235 days). Seven participants (20%) experienced a ≥ 60 -ms increase in QT interval. This led to bedaquiline discontinuation in 2 (6%) participants. The one death (3%) was not considered related to treatment.

References

1. Ndjeka N et al. Safe and effective bedaquiline treatment of drug resistant tuberculosis (DR-TB) within the National Bedaquiline Clinical Access Programme in South Africa. 45th Union World Conference on Lung Health, 28 October – 1 November 2014, Barcelona. The Union/CDC Late breaker session on TB. <http://barcelona.worldlunghealth.org/programme/symposia/body/Programme-2014-50-sympo-19-p-97.pdf> (PDF)
2. Guglielmetti L et al. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. Clin Infect Dis. (2015) 60 (2): 188-194, first published online October 15, 2014 <http://cid.oxfordjournals.org/content/60/2/188.full?sid=d0f4aa8c-28e5-43e2-a5ee-1c263b6dabe5>

Pharmacokinetics and safety of moxifloxacin in children

Polly Clayden, HIV i-Base

Moxifloxacin concentrations were lower in children than adults according to pharmacokinetic (PK) data presented at the 45th Union World Conference on Lung Health. [1]

The Desmond Tutu centre at Stellenbosch University, Cape Town has a large, ongoing study looking at PK and safety of second line anti-TB drugs in HIV positive and negative children with drug resistant (DR)-TB. We have reported data from this programme presented at previous Union meetings. [2, 3]

Late-generation fluoroquinolones – moxifloxacin and levofloxacin – are potent against multi-drug resistant (MDR)-TB. South African guidelines recommend moxifloxacin for children >20kg and >8 years old and levofloxacin for those <20kg and <8 years old.

Moxifloxacin is currently considered the most potent against MDR-TB. It has 90% bioavailability, food has little effect on absorption: about 50% is metabolised by the liver, about 20% is excreted unchanged in urine and 25% in faeces.

Currently only 400 mg tablets are available. The moxifloxacin WHO-recommended daily dose is 7.5 – 10 mg/kg.

Following a standard 400 mg oral dose in adults, PK values have been described in the literature as follows: AUC₀₋₂₄ 40 – 60 ug*h/mL, C_{max} 4 – 6 ug/mL, T_{max} 1 -2 hours, and T_{1/2} of 6–10 hours.

Pharmacodynamic (PD) targets of fluoroquinolones: AUC₀₋₂₄/MIC, target 100 and C_{max}/MIC target 8 – 10.

Steffi Thee presented findings from a nested study in the large MDR-TB drug PK one, conducted to describe the PK of moxifloxacin and to characterise the tolerability and safety of the drug.

HIV positive and negative children 8 – 15 years of age, receiving moxifloxacin as part of routine MDR-TB treatment, were enrolled; those with lab-documented anaemia (Hb <8 g/d/L) were excluded.

Moxifloxacin was dosed at 10 mg/kg and taken on an empty stomach with all anti-TB medications. Intensive PK sampling (0, 1, 2, 4, 8 and 6 or 11 hours) of moxifloxacin at steady state (2 – 8 weeks) was performed. Liquid chromatography-tandem mass spectrometry was used in the evaluation; all assays were conducted at the University of Cape Town Clinical Pharmacology Department.

Routine and laboratory safety assessments were conducted monthly for the first 6 months of treatment, then every 2 months until completion. Liver function tests, creatinine and complete blood cell counts were performed on children receiving antiretrovirals or linezolid; thyroid function was measured in children receiving ethionamide or PAS. Cardiotoxicity was measured. Adverse events were graded using DAIDS criteria.

Dr Thee presented data from 23 children. At baseline they were a median age of 11.1 years (IQR 9.2 – 12.0) and weight of 28.9kg (range 21 – 66 kg). Nine (39.1%) were boys; 13 (56.5%) and 10 (43.5%) were defined as black and coloured ethnicity respectively; 11 (47.8%) had experienced a previous TB episode or treatment; 12 (52.2%) had a known TB source case; 19 (82.6%) had a bacteriologically confirmed TB diagnosis and 4 (17.4%) a probable TB diagnosis; 14 (60.9%) had pulmonary TB, 3 (13.0%) extra-pulmonary TB and 6 (26.1%) had both; 6 (26.1%) children were HIV positive; and 3 (13.0%) had weight-for-age z-score <-2.0%.

Dr Thee reported that the evaluation found the moxifloxacin C_{max} in children nearly approximated that with a 400 mg adult dose but the AUC was substantially lower. Table 1 shows moxifloxacin PK parameters by HIV status, nutritional status and administration method.

Table 1: Moxifloxacin PK parameters by HIV status, nutritional status and administration method

PK Parameter	n	C _{max} (ug/mL)		T _{max} (h)		AUC ₀₋₈ (ug*h/mL)	
		Median (IQR)	p-value	Median (range)	p-value	Median (IQR)	p-value
HIV positive	6	2.83 (2.36 – 2.94)	0.08	2.0 (1.0 – 4.0)	0.33	13.19 (11.8 – 15.9)	0.003
HIV negative	17	3.21 (2.95 – 3.82)		4.0 (1.0 – 8.0)		19.98 (16.71- 25.21)	
WAZ ≥ -2.0	20	3.08 (2.87 – 3.71)	0.41	2.0 (1.0 – 8.0)	0.59	18.76 (16.43 – 23.6)	0.045
WAZ <-2.0 (UWA)	3	2.78 (1.99 – 4.06)		2.0 (1.0 – 8.0)		14.47 (9.95 – 15.9)	
Whole drug	20	2.96 (2.82 – 3.71)	0.29	3.0 (1.0 – 8.0)	0.047	17.36 (14.93 – 23.6)	0.72
Crushed drug	3	3.21 (3.08 – 4.06)		1.0 (1.0 – 2.0)		17.24 (14.47– 19.53)	

Using MIC₉₀ 0.5 mg/L, the PD targets were not achieved: mean AUC₀₋₂₄/MIC(IQR), 56.1 (SD 25.1) vs target 100 and mean C_{max}/MIC(IQR) 6.5 (SD 1.5) vs target 8 – 10.

ECG was performed in 12 children. The mean QT interval was 362 ms (SD 40 ms) and mean QTc 403ms (SD 30 ms). None had QTc interval >450 ms.

One child had a grade 3 ALT elevation possible related to moxifloxacin, all other adverse events were mild and not persistent grade 1 or 2.

Dr Thee suggested that future directions should include: dose optimisation of moxifloxacin in more child-friendly regimens and formulations, investigation into formulation effects on bioavailability, and evaluation of larger cohorts for safety assessment and further investigation into clinical covariates, including HIV coinfection.

C O M M E N T

The large five year study of second-line treatment has an enrollment target of about 300 children. Age matched HIV positive children who are not on TB treatment are enrolled as controls.

The drugs under evaluation are: ethionamide, terizidone, ofloxacin, levofloxacin, moxifloxacin, amikacin, high dose isoniazid (INH), PAS, linezolid and capreomycin. The group will be looking at delamanid and bedaquiline and novel TB drugs as they become available for children.

References

1. Clayden P. Paediatric TB: glimpses of PK data and a potential new approach to drug development. HTB, January/February 2013. <http://i-base.info/htb/20861>
2. Clayden P. Preventing and treating TB in children – more baby steps. HTB, November/December 2013. <http://i-base.info/htb/24037>
3. Thee S. The pharmacokinetics and safety of moxifloxacin in HIV-infected and HIV uninfected children with MDR-tuberculosis. 45th Union World Conference on Lung Health. Barcelona, Spain. 28 October – 1 November, 2014. Symposium abstracts, Saturday, 1 November S49. <http://slideonline.eu/recordings/2014/14union>

TB in the ARROW trial of children on ART

Polly Clayden, HIV i-Base

Incidence of TB disease was highest in the first three months in children with HIV receiving antiretroviral treatment (ART) in the ARROW trial. [1]

TB was associated with lower weight-for-age z-score and lower CD4 percent. Fewer children receiving ART and continuing cotrimoxazole prophylaxis beyond 96 weeks were diagnosed with TB than those that stopped. These findings were shown at the 45th Union World Conference on Lung Health.

In ARROW 1206 Ugandan and Zimbabwean children and adolescents, aged 3 months to 17 years and eligible for ART, were randomised to clinical or laboratory monitoring and to receive standard 3-drug or 4-drug ART. There was a secondary randomisation to continue or stop taking cotrimoxazole after 96 weeks of ART.

Retention and outcomes were excellent in ARROW: only 3% of children were lost to follow-up, 95% remained on first line ART and 96% were alive at the end of the trial.

Angela Cook presented findings from the TB sub-study on behalf of the ARROW trial team.

TB data were collected using a standardised form at enrolment and throughout a median of 4 years follow up. There were 120 TB diagnoses in 111 participants (106 pulmonary, 9 extra pulmonary disseminated and 5 lymphnode). An Endpoint Review Committee adjudicated the diagnoses using all available data but blind to randomised arm; 71% of diagnoses were presumptive.

Of 1206 children, 237 with a previous history of TB were excluded. Of the remaining 969, 900 (93%) had no TB and 69 (7%) confirmed TB. TB incidence decreased over time from initiation of ART: 11.5/100 patient years (py) at 0 – 3 months; 3.1/100 py at 3 – 12 months and 1.4/100 py at >12 months.

In adjusted analysis, lower weight z-score, and lower CD4 percent were associated with TB diagnoses: respectively -3.3 (IQR -4.5 to -2.0) vs -2.1 (-3.2 to -1.2) and 8% (IQR 5 to 13%) vs 13% (7 to 19%) in the TB vs no TB groups. Both comparisons $p < 0.001$.

Dr Cook noted that these results underline the importance of TB screening before starting ART.

In the second part of the sub-study the investigators looked at TB and cotrimoxazole. There were 760 participants randomised to continue cotrimoxazole beyond 96 weeks on ART, of whom 138 with a previous history of TB were excluded. A total of 622 of had a median follow up of 2 years, of this group, 20 (3%) had confirmed TB.

Participants with TB had a median CD4 percent of 22% (IQR 13 – 34%) vs 33% (IQR 27 – 39) in the group with no TB, $p < 0.001$. Of the 20 participants with TB, 15 (75%) were in the group that stopped cotrimoxazole and 5 (25%) in the group that continued, HR (stop: continue) 3.1 (95% CI 1.1 – 8.4) $p = 0.03$. These data add to the evidence of the benefits of prolonged use of cotrimoxazole.

Reference

Crook A et al. Incidence of TB and risk factors in HIV co-infected children in Africa: an analysis of the ARROW trial. 45th Union World Conference on Lung Health. Barcelona, Spain. 28 October – 1 November, 2014. OAP-200-30. Abstract presentations, Thursday, 30 October. S202.

Problems giving current second line TB drugs to children

Polly Clayden, HIV i-Base

Results from a survey presented at 45th Union World Conference on Lung Health reveal an urgent need for child appropriate formulations of second line TB drugs. [1]

Only three second-line TB drugs currently have paediatric formulations. Information is needed on how these medicines are used and the challenges with accurate dosing.

A questionnaire was designed and sent to members of the Sentinel Project on Drug Resistant Tuberculosis in July 2012 (closed end September 2012).

Grania Bridgen from MSF presented findings from the survey on behalf of colleagues from the Sentinel Project, MSF and the Treatment Action Group.

Twenty-one respondents from 13 countries, providing care for more than 400 children answered the survey.

Medications that caused the most difficulty with dosing were: cycloserine (n=7), PAS (n=5), ethionamide (n=4), ethambutol (n=3), quinalones (n=3), PZA (n=2) and terizadone (n=2).

Respondents said that problems related to the large pill burden, duration of treatment and adverse events as well as difficulties splitting adult tablets. All respondents had problems giving the current formulations. For some of the most commonly used second-line drugs there is no standardised protocol, increasing the chances of errors with dosing.

Despite modifications being made to some products – Dr Bridgen gave the example of the PAS dosing spoon – these might not reach those that need them.

The Sentinel Project is working on Target Product Profile for second-line drugs for children to help minimise delays with child appropriate formulations.

C O M M E N T

This survey highlights the practical difficulties associated with giving second-line TB drugs with children, where appropriate formulations are not usually available.

References

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TREATMENT ACCESS

Morocco's acceptance of EU patent law threatens millions of lives

Othoman Mellouk, ITPC-MENA

On 25 January 2015, civil society organisations in Morocco, concerned about the lives of millions of citizens, issued a press statement because the Moroccan Patent Office (Office of Industrial and Commercial Property - OMPIC) has formalised an agreement with the European Patent Office (EPO) to validate European patents in Morocco on 1 March 2015.

This means that patent applications and patents granted in Europe will be legally recognised as Moroccan patents and will be subject to Moroccan law. Morocco is the first country outside of the European Patent Organisation to validate the European patent in its territory.

The International Treatment Preparedness Coalition in North Africa-Middle East (ITPC-MENA), Association de Lutte Contre le Sida (ALCS) and the Collective for the Right to Health in Morocco (CMDS) denounce such agreement designed primarily to strengthen the multinational companies monopolies on the medicines market in Morocco and block the use of lifesaving generic drugs which will have a huge impact on the right to health and access to medicines.

According to Himmich Hakima, Chair of ALCS: "Morocco and Europe have diametrically opposed interests in the protection of intellectual property. European countries are exporters of innovation and have an interest in protecting the most of their industry. Morocco is a consumer of innovation. Instead of comparing to Europe we need to learn from countries such as Brazil, India or the Egypt who apply the protection required by the World Trade Organisation while protecting the public interest including access to health and medicine. These are the main recommendations of international organisations such as the WHO."

The European Patent Office is known for its permissive patent granting. In 2013, 266,000 patent applications were filed in Europe compared to only 1,096 requests in Morocco. In Europe, multinational companies routinely use the patenting of medicines from minor changes that do not really constitute an invention, lack novelty and are not considered patentable under WTO standards.

With this new agreement, OMPIC will treat as many patent applications as in Europe within a period of 18 months set by the law and with threats of sanctions imposed by the Free Trade Agreement with the United States for each day of delay. Mellouk Othman, Advocacy Officer at ITPC-MENA stated: "With such pressure on OMPIC it is clear that many abusive patents will be issued with a consequent monopoly and market exclusivity granted to multinationals for a period of 20 years on drugs that do not deserve it and for which the health system and the citizen will pay a heavy price." In addition: "The principle of national sovereignty, according to the WTO requires that the patent applicant makes the process of filing an application with the national authorities of the country where he seeks protection. This agreement also represents a real turning on European tutelage of our patent system."

For example, the Egyptian patent office recently rejected the patent application for Gilead's HCV drug sofosbuvir on the grounds of lack of innovation and novelty; and concluded that sofosbuvir does not deserve the grant of an exclusive right to 20 years. Thus, Egypt will be able to use the generic versions of the drug. For cons, the European Patent Office has validated despite the lack of innovation and novelty.

The proliferation of IP and Trade Agreements in Morocco, we are entitled to ask whether the policy in the country is consistent with the efforts of the Ministry of Health to lower drug prices and expand access to health insurance. The current policy seems to favor the profits of the

pharmaceutical lobby to the detriment of citizens' interests while ignoring the recommendations of public health agencies such as WHO.

ITPC-MENA, ALCS and CMDS request the freezing of the agreement and the creation, like in other developing countries, of multisectoral national commission including the Ministry of Health and the civil society to develop a National Intellectual Property Policy that takes into account the international obligations concerning the protection but also the level of development of the country and sensitive social concerns including access to medicine and health. The three organisations also call for strengthening South-South cooperation with countries and patent offices that have the same interests and priorities rather than losers partnerships with industrialised nations.

Source:

ITPC-MENA press release. Guardianship of the Europe on the patent system of Morocco puts lives of millions of citizens in danger. (24 January 2015).

<http://www.itpc-mena.org>

Global Fund releases end-2104 numbers

Global Fund Observer

The number of people receiving antiretroviral therapy through programmes supported by the Global Fund reached an estimated 7.3 million by the end of 2014, a 20% increase over a year earlier.

A total 450 million insecticide-treated nets to prevent malaria were distributed, up 25% over 2013's total of 360 million.

The number of TB cases detected and treated rose from 11.2 million a year ago to 12.3 million at the end of 2014, a 9% increase.

Other key results numbers announced by the Fund on World AIDS Day, 1 December, show year-on-year increases ranging from 4% to 38% (See Table1). [1]

Table 1: Cumulative results from programmes to which the Global Fund contributed

	Results to December 2014	Results to December 2013	Year change
No. of people receiving ART	7.3 million	6.1 million	+ 20%
TB smear-positive cases detected and treated	12.3 million	11.2 million	+ 9%
MDR-TB cases treated	150,000	108,908	+ 38%
No. of condoms distributed	4.9 billion	4.5 billion	+ 9%
No. of HIV counseling and testing sessions conducted	390 million	306 million	+ 27%
No. of malaria ITNs distributed	450 million	360 million	+ 25%
Structures covered by IRS	55.0 million	48.3 million	+ 14%
Malaria cases treated	470 million	390 million	+ 21%
HIV behavioral change communications	450 million	412 million	+ 9%
No. of women receiving PMTCT treatment	2.7 million	2.4 million	+ 13%
Care and support services provided	27.0 million	24.6 million	+ 10%
Care and support for OVC	7.2 million	6.9 million	+ 4%
Treatment for STIs	21.0 million	19.6 million	+ 7%
People treated for TB/HIV	11.0 million	9.4 million	+ 17%
Person episodes of training for health or community workers	15.6 million	14.9 million	+ 5%

In a news release accompanying the announcement of the results, the Global Fund said that the numbers "show significant movement towards common milestones in HIV response, articulated well in a study recently released by UNAIDS that calls for fast-tracking the HIV response to end the epidemic by 2030."

The news release also noted the accelerated efforts against malaria and progress in the response to TB.

Source

Global Fund Observer Newsletter, issue 257. (11 December 2014).
<http://www.aidspace.org/node/3074>

Ref: Global Fund Reports Results – 2014 01 December 2014

http://www.theglobalfund.org/en/mediacenter/newsreleases/2014-12-01_Global_Fund_Reports_Results_2014

ANTIRETROVIRALS

Dolutegravir and Trimeq approved in England

Simon Collins, HIV i-Base

On 14 January 2015, NHS England published the long awaited policy on dolutegravir and the fixed dose combination (FDC) of dolutegravir/abacavir/3TC (Trimeq). [1]

The NHS policy states two reasons why dolutegravir has the potential to improve care:

Firstly, that it reduces levels of HIV virus in the body quickly. This is the main aim of HIV treatment.

Secondly, that it causes fewer side effects than some other HIV drugs. This includes a much lower risk of common side effects such as mood changes, depression, anxiety, disrupted sleep and suicidal thoughts. Overall, this means the treatment is better tolerated and improves patient safety.

The evidence for these benefits came from large randomised studies. Studies looking at switching people on stable therapy are still ongoing.

The guidelines detail situations when dolutegravir can be prescribed, both for treatment-naïve and -experienced patients.

1. Patients unable to tolerate first line therapy

- Patients who are not suitable for or who do not tolerate efavirenz based first line therapy due to demonstrated toxicity, intolerance, adherence, treatment failure or resistance as agreed in the multi-disciplinary team (virtual clinic). Dolutegravir is a treatment option for this patient group.
- This policy recommends that where dolutegravir is used, it should be combined with the lowest cost, clinically indicated backbone.
- The cohort of patients requiring alternative to first-line therapy is expected to be no more than 30% of the total treated patient cohort. Dolutegravir is now one of the options for these patients.

2. Patients failing treatment and those with resistance

- Dolutegravir is approved for use in patients requiring an integrase inhibitor due to recorded treatment failure or resistance.
- In treatment experienced and integrase inhibitor naïve patients at a dose of 50mg daily.
- In treatment experienced and integrase resistant patients at a dose of 50mg twice daily.

London prescribing guidelines were also updated on 14th January to include the new recommendations for dolutegravir and Trimeq. [2]

C O M M E N T

It is good that NHS executives finally agreed that specialised services clinical commissioning policies approved for publication will be available on the NHS England website. However, this has involved a long and protracted review and final review process given that the European Medicines Agency (EMA) approved dolutegravir almost a year ago. [3]

A lot of people involved in providing HIV care worked hard to help this review and feedback to policy drafts from various stakeholders hopefully helped this process.

Dolutegravir was approved in Scotland in May 2014. [4]

Trimeq was approved in Europe in September 2014. [5]

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London prescribing guidelines updated to include dolutegravir and Triumeq

Simon Collins, HIV i-Base

On 14 January 2015, London guidelines for first-line ARV therapy were updated to include dolutegravir and Triumeq and published as a PowerPoint slide set. [1]

This January 2015 update was to reflect new NHS England prescribing policy for dolutegravir. [2]

- In London, dolutegravir can now be prescribed as an option for first-line therapy when neither efavirenz nor raltegravir are appropriate. Because of its higher price, this requires referral to a multi-disciplinary team or virtual clinic. (Slide 14).
- The guidelines do not recognise a clinical advantage of fixed dose combinations for most patients in preference to prescribing recommendations. (Slide 15).
- Dolutegravir can also be considered as an option for people who are switching treatment due to side effects or intolerance as these people are not defined as being stable on therapy. (Slide 23).
- Dolutegravir should be prescribed in combination with Kivexa (abacavir and lamivudine) unless this is contraindicated. Dolutegravir plus Kivexa is recommended rather than the single pill fixed dose combination (Triumeq). (Slide 24).
- However, Triumeq can be prescribed for some patients if this is the outcome of the virtual clinic. (Slides 24 and 26).

A 6 month prospective audit is planned for all patients starting ART from December 2014. An audit of those switching within six months is also planned. Centres using higher proportions of non-efavirenz based regimens will have external audit of their virtual review and audit clinic. (Slide 16)

Since 2011, the London tender process have already saved more than £10 million which is equivalent to approximately 5.2% annual savings from the ARV drug budget. The contract from 2014 is expected to save a further £ 4.8 million. (Slide 2).

The trade name for dolutegravir is Tivicay and the trade name for the fixed dose combination is Triumeq. Both are manufactured and marketed by ViiV Healthcare.

C O M M E N T

This is an update to the current guidelines published in July 2014 (applied from April 2014). [3]

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Adequate cerebrospinal fluid exposure of efavirenz when dosed at 400 mg

Polly Clayden, HIV i-Base

Although 400 mg efavirenz (EFV) gives cerebrospinal fluid exposure (CSF) exposure of EFV above that required for HIV suppression, exposure of metabolites might still be within the concentration range associated with toxicities – according to findings from the ENCORE1 trial.

ENCORE1 demonstrated that 400 mg of EFV once daily is non-inferior to the standard 600 mg dose. [1]

ENCORE1 participants, at five participating sites in London, Berlin, Bangkok and Khon Kaen, were eligible to enter a CSF substudy. The aim was to look at CSF exposure, as a surrogate for CNS exposure, of EFV and its major metabolites after at least 12 weeks of receiving the EFV and compare the two doses.

The results were published in Clinical Infectious Diseases, 25 December 2014, authored by Alan Winston and colleagues from the ENCORE1 CSF Substudy Team.

Between 12 and 24 weeks of starting ART in ENCORE1, the participants underwent CSF examination at least 8 hours after dosing. Cerebral imaging and assessments of blood clotting were performed as part of clinical practice before a lumbar puncture examination. The investigators made the following analyses on CSF samples: total protein; assessment of EFV; 8OH-EFV, and 7OH-EFV; and CSF HIV RNA level. Immediately before the CSF examination, blood sampling was done in order to assess plasma EFV, 8OH-EFV and 7OH-EFV concentrations.

Baseline characteristics were similar in the 400mg and 600 mg groups. CSF examination was successful in 28 participants (14 in each dosing group).

The investigators reported that mean CSF protein was 0.40 g/dL (range 0.24 – 1.02 g/dL). Plasma HIV viral load was undetectable in all participants: <5 copies/mL in all but one participant who had <10 copies/mL. CSF viral load was also undetectable in all with corresponding values.

Geometric mean (GM) CSF EFV, 7OH-EFV and 8OH-EFV concentrations for the 400 mg and 600 mg dosing groups were respectively: 16.5 (90% CI 13 – 21) and 19.5 (90% CI 15 – 25) ng/mL; 0.6 (90% CI 0.4 – 0.9) and (90% CI 0.4 – 1.0) ng/mL; 5.1 (90% CI 4.0 – 6.4) and 3.1 (90% CI 2.1 – 4.4) ng/mL.

CSF EFV concentration in all participants was greater than the proposed 50% maximal inhibitory concentration for wild type virus of >0.51 ng/mL. 8OH-EFV concentration in CSF was greater than a proposed toxicity threshold of >3.3 ng/mL in 11/14 and 7/14 participants in the 400 mg and 600 mg groups respectively.

CSF concentration was significantly associated with plasma concentration, $p < 0.001$, and cytochrome P450 2B6 genotype. CSF EFV GG to GT/TT geometric mean ratio (GMR), 0.56 (90% CI 0.42 – 0.74). CSF 8OH EFV concentration was not, $p = 0.242$. GG/GT GMR, 1.52 (90% CI 0.97 – 2.36).

The authors also provided a detailed discussion on EFV CNS toxicities in the article. The substudy included an exploratory analysis of associations between CSF 8OH EFV exposure and Depression Anxiety Stress Scales, an EFV symptom questionnaire (ESQ) and functional health status at 48 weeks.

There were associations between CSF 8OH EFV exposure and patient reported toxicities frequently associated with EFV: ESQ at 48 weeks, Spearman Correlation Coefficient 0.13, $p = 0.5$. But the authors noted that these findings are limited by the post hoc nature of the analysis, the small number of participants and the predominately male Asian and white people enrolled.

They suggested that the pharmacogenomic observations in the substudy might provide plausible explanations for some of their pharmacokinetic findings. Higher CSF EFV exposure was seen in participants with GT or TT genotypes in CYP2B6, so for those with slower EFV metabolism genotype, plasma exposure is higher compared to those with faster – as expected CSF is also higher. But, such a signal was not observed for CSF 8OH EFV exposure, where CSF concentrations were similar between genotypes.

They postulated that pharmacokinetic processes involved in CSF 8OH EFV exposure might be subject to a saturation effect by which exposure to the metabolite is not dependent on plasma EFV exposure or CYP2B6 genotype. Instead, they suggest, this could be a spillover from plasma 8OH EFV or local CNS production of 8OH EFV where this metabolite becomes “trapped” within the CNS compartment.

The authors also discussed EFV autoinduction – but did not conclude that a differing effect on autoinduction is a plausible explanation for their findings. An upregulation in efflux transporters that was dependent on EFV dose and affected the removal of 8OH EFV from the CNS might be another theoretical explanation for their findings, they suggested.

In conclusion, they write that in the main ENCORE1 study, there were no differences in the number of participants reporting adverse events, but more EFV-related ones were observed in the 600 mg than the 400 mg group. The authors believe that their substudy provides one plausible explanation for these findings.

C O M M E N T

Although EFV 400 mg was non-inferior to 600 mg, the reduction in EFV-associated adverse events was modest and the authors above suggest this possible explanation.

Last year, three leading HIV doctors suggested that the dominant role of EFV in first line therapy should be reconsidered. [3] They noted that “this should not only happen in high-income countries but ideally also in low-income settings, if alternative drugs are available, and this recommendation should be reflected in the treatment guidelines of the WHO and both governmental and non-governmental organisations”.

It is good to see that we finally have guidance for dolutegravir use in the UK. As experience with this drug grows and the price decreases, there will be increasing interest in using dolutegravir in both high and low-income countries as a more tolerable alternative to EFV.

For low-income countries, EFV is likely to remain the preferred first-line treatment for a while. WHO adoption of the 400 mg dose has been subject to considerable discussion, particularly concerning the robustness of the lower dose for people taking TB treatment and for women in the third trimester of pregnancy.

PK studies to look at efavirenz drug levels in these situations are still not underway.

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PREGNANCY & PMTCT

Three drug regimen superior for preventing vertical transmission in the PROMISE study

Polly Clayden, HIV i-Base

Taking three drug ART in pregnancy was more effective in preventing mother-to-child transmission than taking one drug during pregnancy, another in labour and two after delivery – according to interim data from the PROMISE (Promoting Maternal-Infant Survival Everywhere) study.

The findings were reported on 4 November 2014 during a scheduled interim review of PROMISE by an independent data and safety monitoring board (DSMB). The US National Institutes of Health issued a press release explaining the results on 17 November 2014. [1]

PROMISE is a multinational from the IMPAACT Network, [2] which has been ongoing since 2010, and is looking at the best way to reduce the risk of mother-to-child transmission during pregnancy and after delivery in asymptomatic women with CD4 >350 cells/mm³ (or national CD4 threshold for initiating treatment).

The study includes two years follow-up from after the last child is born to look at the safety and efficacy of antiretroviral regimens taken during the breastfeeding period. It is also looking at maternal health after the breastfeeding period in women who either stop or continue taking ART.

All infants receive a daily dose of nevirapine until 6 weeks of age, and those who are HIV-infected receive ART.

Women in the study were randomly assigned to receive: AZT from ≥ 14 weeks of pregnancy, and a single dose of nevirapine during labour, and two weeks of tenofovir and FTC after delivery (WHO Option A); or one of two triple ART regimens from ≥ 14 weeks (WHO Option B or Option B+). The ART regimens are lopinavir/ritonavir plus either 3TC/AZT or tenofovir/FTC.

At the time of the DSMB review, the study had enrolled >3,500 pregnant or post-partum women and >3,200 HIV-exposed infants of the women in India, Malawi, South Africa, Tanzania, Uganda, Zambia and Zimbabwe. HIV transmission data to 14 days post partum were evaluated.

The DSMB found that there was a significantly lower rate of transmission during pregnancy or delivery in the group who received an ART regimen than among those who received Option A.

Only 0.5% of infants whose mothers received the 3TC-containing regimen and 0.6% of infants whose mothers received the tenofovir-containing regimen were infected with HIV, compared to 1.8% of infants whose mothers received Option A.

The review also concluded that the 3TC-containing ART regimen appeared to be safer than the other strategies. Women who received 3TC experienced fewer severe adverse pregnancy outcomes including very low birth weight, very preterm delivery, stillbirth, spontaneous abortion or major birth defects. There were also fewer infant deaths within 14 days of birth those than in those in the tenofovir or Option A groups. Preterm delivery was the most common cause of death.

But, there were a greater number of less severe outcomes, including birth weight <2,500 grams and preterm delivery at < 37 weeks gestation, in infants whose mothers received ART than those whose mothers received Option A.

The DSMB recommended that these results be made public and the investigators, women in the study who remain pregnant, and their health care providers determine the best regimen with which to continue.

The other parts of the study will remain unchanged and continue.

C O M M E N T

Although Option A was still an option for women not yet eligible for treatment when this study was designed, several critics questioned the ethics of giving pregnant women a regimen below the standard of care in their country, as WHO and national guidelines abandoned it. [3]

It is also unclear why the 2012 review of PROMISE did not recommend stopping the suboptimal arm earlier.

Although transmission risk was very low across the trial arms, unsurprisingly three-drug ART does better at 14 days from delivery. However, the question of whether women should continue or stop ART after breastfeeding remains unanswered. Several national programmes now recommend lifelong ART for all pregnant women regardless of CD4 count (Option B+), largely to minimise the complexities of stopping and restarting treatment.

The more surprising finding was the greater frequency of adverse outcomes in the group receiving tenofovir-based ART. It is notable that the regimen used in PROMISE included lopinavir/ritonavir. Hill et al recently reported approximately 30% increases in tenofovir AUC in a literature search to determine the effects of boosted antiretrovirals on tenofovir plasma concentrations. The authors noted that tenofovir toxicity might be over estimated in clinical trials were it is only combined with boosted antiretrovirals.

The efficacy of tenofovir 300 mg once-daily was established in trials with EFV, which does not increase tenofovir drug levels. The WHO recommended first line regimen for pregnant women is EFV, 3TC and tenofovir.

The PROMISE interim findings have been submitted to CROI as a late breaker.

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SIDE EFFECTS & COMPLICATIONS

CMV associated with 50% increased risk of non-AIDS related mortality in HIV positive people

Gareth Hardy, HIV i-Base

Coinfection with cytomegalovirus (CMV) infection may be associated with a 50% higher risk of non-AIDS defining mortality compared to HIV people who are CMV negative, according to an analysis from Italian ICONA cohort study, published in the January edition of JID. [1]

Miriam Lichtner and colleagues at Sapienza University of Rome, Italy, investigated patients from the Italian multi-centre, prospective observational ICONA Foundation Study cohort, who were naïve to ART at enrolment. Lichtner et al assessed clinical events and causes of death in a subset of 6,111 patients who had had at least one CMV IgG antibody test and had at least one follow up visit since their CMV test. Patients who had any reported CMV-related disease or non-AIDS-defining event were excluded from the study analysis.

CMV antibodies were detected in 5119 study participants (83.3%). In multivariable logistic analysis, being CMV positive was associated (adjusted odds ratio) with age per 10 year increase (aOR 1.42; 95%CI: 1.33 – 1.52, $p < 0.0001$), MSM sex vs IV drug use (aOR 1.67; 95%CI: 1.36 – 2.06, $p = 0.0001$) and a higher CD4 count at baseline (aOR 1.04; 95%CI: 1.02 – 1.06, $p = 0.0005$). Being CMV positive was negatively associated with white ethnicity (aOR, 0.51; 95%CI: 0.39 – 0.66, $p = 0.001$).

During a median 5.2 years of follow up, 413 participants experienced an AIDS-defining event and 77 died as a result of an AIDS-related disease. No significant differences were seen in the frequency of AIDS-defining events or AIDS-related deaths between CMV-seropositive and CMV negative individuals.

In contrast, severe non-AIDS defining events or non-AIDS related deaths were significantly related to CMV coinfection. During a median 5.6 years of follow up, 326 patients experienced severe non-AIDS defining events and 12 patients died from non-AIDS related diseases. The investigators estimated the proportion of patients reaching either end point at 10 years as 6.2% (95%CI: 4.1% – 8.3%) for CMV seronegative patients and 8.9% (95%CI: 7.7% - 10.1%) for CMV seropositive patients ($p = 0.0058$). Even after controlling for a number of potential confounding factors (including age, sex, ethnicity, HCV or HBV status, mode of HIV transmission, time from HIV diagnosis, CDC disease stage, use of ART, CD4 count or CD4/CD8 T cell ratio), being CMV positive remained an independent risk factor for severe non-AIDS defining events or non-AIDS related deaths (adjusted hazard ratio [HR] 1.53 995% CI, 1.08 – 2.16, $p = 0.16$).

In multivariate analysis, being CMV positive was not associated with non-AIDS related malignancies or nonvascular neurological diseases. In contrast, CMV positivity was an independent risk factor for cardiovascular and cerebrovascular diseases (adjusted HR, 2.27 [95% CI, 0.97 – 5.32, $p = 0.058$).

The authors concluded that CMV infection might play a significant role in the non-AIDS related morbidity and mortality of HIV positive people. There was a striking association between being CMV positive and risk of cardiovascular and cerebrovascular disease. There is increasing evidence that inflammatory processes may play a role in these diseases and CMV has been directly implicated in cardiovascular disease such as atherosclerosis. It is therefore possible that subclinical CMV activity may contribute to the inflammation-mediated pathology of vascular disease in people with long-term HIV infection.

C O M M E N T

The impact of other coinfections is focus of research by several groups.

The mechanism for any association remains unclear as recent HIV studies looking at this potential therapeutic role of anti-inflammatory drugs have not shown clinical benefits.

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Impact of smoking on life expectancy in HIV infection

By Gareth Hardy, HIV i-Base

Smoking may double the risk of mortality for HIV positive people according to results from a large collaborative HIV cohort study of people who have been on ART for more than one year.

This is according to results presented by Marie Helleberg and colleagues from the University of Copenhagen in Denmark, and published in the January issue of AIDS. [1]

Helleberg et al show that while the life expectancy of a non-smoking, HIV positive, 35 year-old male with a CD4 count above 200 and viral load below detection for more than one year, is similar to that of the general population, the life expectancy of a similar male who smokes is 8 years shorter. These results confirm those of a previous study that investigated smoking-associated mortality in HIV positive people in Denmark. [2]

The investigators presented data on 17,995 HIV positive individuals, from eight different cohorts in Europe and North America, who were followed for 79,760 person years. In three cohorts, individuals were categorised as smokers (current or previous) or non-smokers. In the remaining five cohorts, individuals were categorised in more detail as current, previous or never smokers. In order to calculate the number of life years lost due to HIV, the life expectancy in the cohorts was compared to that of the male general French population. The study lacked statistical power to determine life expectancy in women, therefore the results on loss of life years and life expectancy can only be extended to the male population.

HIV positive individuals were eligible for inclusion in the analysis if they started ART (with at least 3 drugs), were alive and under follow up 365 days after ART initiation, and had data on smoking status. Follow up for each person began at the time that smoking status was determined or 365 days after starting ART, whichever was later. 71.3% were men, 70.6% had a viral load below 400 copies/ml and 56.2% had a CD4 count above 350 cells/mm³ at baseline.

The investigators estimated excess mortality rates using a formula where the mortality rate of smokers was subtracted from the mortality rate of non-smokers. Mortality rate ratios were calculated using Poisson regression analysis adjusted for sex, age, mode of HIV transmission, year of ART-initiation, years on ART, CD4 count at baseline and AIDS at ART initiation.

The all-cause mortality rate for smokers was 7.9 per 1000 person years (95%CI: 7.2-8.79) and for non-smokers was 4.2 (95%CI: 3.5 – 5.0) and the adjusted mortality rate ratio (MRR) for smokers versus non-smokers was 1.94 (96%CI: 1.56 – 2.41). When individuals were stratified according to sex, route of HIV transmission, CD4 count or viral suppression at baseline, it did not affect the MRR of smokers versus non-smokers.

Cause of death could be determined for 90% of 520 cases. Out of those cases, AIDS-related causes of death were determined for 29% of cases with a mortality rate of 1.6 per 1000 person years (95%CI: 1.3 – 1.9). Non-AIDS related causes of death were determined for the remaining 71% of cases with a mortality rate of 4.6 per 1000 person years (95%CI: 4.2 – 5.1). In smokers the rate of non AIDS-related deaths was higher than in non-smokers with a MRR of 2.61 (95%CI: 1.88 – 3.61).

Assessment of the rates of death by specific causes further revealed significant differences between smokers and non-smokers. Comparing smokers with non-smokers the rates of non AIDS-related deaths were significantly higher with a MRR of 2.61 (95%CI: 1.88 – 3.61), in which deaths related to cardiovascular disease, non-AIDS malignancies and liver disease were all significantly higher in smokers. Lung cancer accounted for 36% of non-AIDS malignant deaths, and occurred exclusively in smokers. Of the non-AIDS malignant deaths, 50% were due to cancers associated with smoking and 96% of those occurred in smokers.

Smoking also had a substantial effect on life expectancy. The number of life years lost was calculated for each age bracket from 25-65, in 10-year intervals. Data for those above 65 were pooled. The greatest reduction in life years was observed for younger cohort participants. The investigators speculate that this is partly because the health impacts of smoking only manifest after several years of exposure and partly because middle and older age persons are less likely to take up smoking. Life expectancy for HIV positive men aged 35 was found to be 5.9 years shorter (95%CI: 4.9 – 6.9) than the same age bracket in the general population. In contrast life expectancy for HIV positive smokers in this age bracket was found to be 7.9 years (95%CI: 7.1 – 8.7) shorter. For those aged over 65 the loss of life years associated with HIV was 2.9 years and the loss of years associated with smoking was 6.6 (95%CI: 6.0 – 7.2) years. Therefore while the number of life years lost due to HIV-infection declines with from the 35 years age bracket to 65 years, the number of life years lost due to smoking remains fairly constant. When the investigators looked at excess mortality rates associated with smoking or HIV-infection, they both increased with age. However the increase in excess mortality rate that occurs with age, was much greater in association with smoking than with HIV-associated factors.

In this study, smoking was associated with a two-fold increase in mortality rate, and the excess mortality rate in smokers was mostly accounted for by non-AIDS malignancies and cardiovascular disease. The investigators point out that their observation that the risk of death in previous smokers is substantially lower than that in present smokers, suggests that smoking cessation programs may have potential benefits in HIV care. While this study had limited data on the effects of current versus previous smoking, the investigators have shown in a different study that previous smokers had similar mortality rates to those who had never smoked. [2]

In addition, the rate of cardiovascular disease in HIV positive individuals greatly decreases with time since ceasing smoking. [3]

The results of these studies contrast with those conducted in the pre- or early-ART era, which found that there was little impact of smoking on mortality in HIV positive people. [4]

The investigators of this study suggest this is because the reduction in life years lost to AIDS has steadily diminished as the ART era has progressed, while at the same time the impact of smoking and other life-style risk factors is likely to increase, as HIV positive people live longer and age.

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HEPATITIS C

India rejects Gilead's patent application for sofosbuvir

Simon Collins, HIV i-Base

On 20 January 2015, the Indian court made a landmark decision to reject a patent application for the hepatitis C drug sofosbuvir. [1]

This decision could enable an affordable option for effective treatment globally, especially for people in resource-limited settings. It may also enable access for people in middle- and high-income settings who are unable to afford treatment, or where access to treatment is restricted.

This is a victory for civil society activists in India, including the Lawyers Collective, the Hepatitis Coalition of Nagaland, and Network of PLHIV living in the Asia Pacific region (APN+) who filed a challenge to the patent in India. [2]

The main challenge was that sofosbuvir lacks novelty, or inventive manufacturing steps required under the Indian Patents Act.

Existing patents in many countries will still block access to generic sofosbuvir. This includes in South Africa, where a joint press release from the Treatment Action Campaign, Section 27 and Médecins Sans Frontières noted "...sofosbuvir is not yet registered or available in South Africa, and existing patent barriers could hinder the country from looking for multiple generic sources of the drug in order to get the most affordable prices". [1]

Originator manufacturer Gilead has been widely criticised for setting a price for sofosbuvir that will dramatically restrict use even in Western countries. A 12-week course costs £34,000 in the UK and \$84,000 in the US. Even with cure rates, Western economies will only be able to treat a fraction of people with hepatitis C, many of whom are not yet diagnosed.

i-Base have also reported the analysis from Hill and colleagues showing that the production and manufacturing costs for sofosbuvir and other direct acting HCV drugs, are estimated to be less than \$150 for a three-month course of treatment. [3]

C O M M E N T

Last week Gilead stepped up pressure on India and is trying to reverse the decision of the Indian Patent Office through the courts. The company is currently also putting pressure on the Department of Industrial Policy in India, which oversees the patent office, using the argument that there will be no problem accessing sofosbuvir in India (or in other developing countries) because last September Gilead issued a voluntary license to Indian generic companies enabling them to produce generic versions for some countries, determined by Gilead.

This license has been criticised by many groups of civil society and experts working in intellectual property and access to medicines. The voluntary license has a number of problems that call into question whether Gilead will really allow access, or just inhibit open generic competition, which is proven to be the most effective way to bring down the price of medications. Problems with the voluntary license include:

- **The exclusion of 50 developing countries from the territories covered by the voluntary license (mainly middle-income countries). These include countries severely affected by the HCV epidemic that will not be able to afford the prices charged by Gilead. This is even if there is no patent protection in those countries,**
- **Banning the sale of raw materials used in the manufacture of generics outside few Indian generic producers selected by Gilead in the voluntary license, including exclusion of manufacturers in countries where there is no patent eg Egypt,**
- **Anti-diversion measures in total violation of the principles of human rights and medical ethics disclosing confidential data of the patients. Even in countries included in the license these measures permit the exclusion of all people not eligible for government programmes to access treatment, as well as people who are treated in the private sector and foreign residents.**

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Hepatitis C combination from AbbVie licensed in the UK: ombitasvir/paritaprevir/ritonavir (Viekirax) and dasabuvir (Exviera)

Simon Collins, HIV i-Base

On 19 January 2015, AbbVie announced that its direct acting antiviral (DAA) hepatitis C drugs are now available in the UK, following EU marketing authorisation. [1]

The approvals were for the combination tablet of ombitasvir/paritaprevir/ritonavir (brand name Viekirax) and single compound dasabuvir (brand name Exviera).

The indication for both drugs is for use with or without ribavirin in patients with genotype 1 (GT1) chronic hepatitis C virus (HCV) infection.

The combination tablet ombitasvir/paritaprevir/ritonavir is also licensed for use with ribavirin in non-cirrhotic, genotype 4 (GT4) chronic HCV patients.

The combined formulation contains ombitasvir 12.5 mg (NS5a inhibitor, previously ABT-450), paritaprevir 75 mg (NS4/4A protease inhibitor) and ritonavir 50 mg (pharmacokinetic booster). The recommended oral dose is two tablets taken once daily with food.

Dasabuvir 250mg is a non-nucleoside NS5B polymerase inhibitor. The recommended oral dose is one tablet, twice daily (morning and evening). Dasabuvir must always be administered together with ombitasvir/paritaprevir/ritonavir.

The efficacy of Viekirax has not been established in patients with HCV genotypes 2, 3, 5 and 6; therefore Viekirax should not be used to treat patients infected with these genotypes.

There are no data on the use of Viekirax and ribavirin in patients with HCV genotype 4 infection, with compensated cirrhosis and therefore the optimal treatment duration has not been established. Based on in vitro antiviral activity and available clinical data in HCV genotype 1, for people with HCV genotype 4 and compensated cirrhosis, a conservative treatment duration of 24 weeks is recommended.

Please see full product specifications for further details. [2, 3]

C O M M E N T

This press release from AbbVie of UK availability is perhaps premature given the protracted NHS process to decide on access to new drugs and that a price has yet to be announced.

It seems likely that AbbVie will be interested setting comparable drug prices to Gilead rather than using the opportunity to bring competition to this market,

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PREVENTION

HIV prevention budget for 2015 slashed by 50%, then rapidly reinstated

Simon Collins, HIV i-Base

According to a policy brief by the National AIDS Trust, several recent government announcements suggested that remaining central government budgets for HIV prevention budget were likely to be slashed in 2015. [1]

A community response led by National AIDS Trust that included sending more than 1500 signatories of an online petition sent to Jane Ellison, Minister for Public Health Minister, led to a written response on 22 December stating that the Government will protect funding for the National HIV prevention programme in England. [2]

The letter also stated: “...while the HIV prevention budget will be maintained, we do want to be more ambitious in our plans to prevent HIV and to explore new and more innovative ways of doing things... Improving the way we deliver the HIV prevention programme will be part of our longer-term strategy for sexual and reproductive health which we plan to announce in the New Year.”

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Grassroots demand grows for early access to PrEP in the UK

Simon Collins, HIV i-Base

In November 2014, a community statement calling for wider access to PrEP highlighted the importance of early results from the UK PROUD study that had been released the previous month. [1]

By 21 January 2015, the statement (printed below) had collected more than 1280 individual and organisational supporters.

The document was drafted by six HIV community organisations to update an earlier community statement in support of the PROUD study, and to reflect the recent results showing that PrEP works for gay men in the UK who are at high risk of HIV. PrEP involves taking a single daily pill containing two HIV drugs, which with good adherence is likely to have >95% efficacy.

The NHS advisory group working on access to PrEP, were also met with a lively demonstration organised by the direction action group ACT-UP London, some of whose members are participants on the PROUD study. [2]



ACT-UP outside Wellington House, SE1. Photo: Mike Kear.

The ACT-UP statement called for immediate access, highlighting that with 500 people are diagnosed with HIV each month in the UK, none of whom have access to PrEP.

Activist Seán McGovern said the two-year wait was unacceptable: “We already know that PrEP is highly effective in stopping infection when taken correctly – and yet in the UK only the 545 study participants are currently able to take it. There were 6,000 new HIV diagnoses in 2013 alone. Each year that we wait means consigning a huge number of people to infections that could be prevented.”

Currently, access to PrEP through the NHS is restricted to 545 participants in the PROUD study.

The early efficacy results in PROUD led to a change in the study design, offering immediate PrEP to all participants. [3] More detailed results are expected to be presented in February at the Conference of Retroviruses and Opportunistic Infections (CROI), together with results from the French IPERGAY study. [4]

Statement on PrEP from community organisations working on HIV prevention

Two European studies of pre-exposure prophylaxis (PrEP), PROUD (i) and IPERGAY (ii), reported early results in October 2014. Both studies showed that PrEP was so effective at preventing HIV transmission that everyone in these studies has now been offered PrEP. The comparison arms, which respectively offered delayed PrEP or a placebo, have been closed.

In light of this news, together with data on continued high rates of new infections (iii), the NHS urgently needs to make PrEP available.

Although an NHS England process to evaluate PrEP is underway, any decision to provide PrEP will probably not be implemented until early 2017, which is too long to wait.

We are calling for earlier access to PrEP. The NHS must speed up its evaluation process and make PrEP available as soon as possible. Furthermore, we call for interim arrangements to be agreed now for provision of PrEP to those at the highest risk of acquiring HIV.

This statement is endorsed by GMFA, NAT, THT, NAM, Yorkshire MESMAC, Positively UK, HIV Prevention England and the Lesbian and Gay Foundation. Other organisations can sign up by contacting Yusef Azad at NAT: yusef.azad@nat.org.uk.

Notes

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New York announces new policy to dramatically reduce HIV incidence by 2020

Simon Collins, HIV i-Base

On 13 January 2015, a new strategy was announced to reduce HIV incidence in New York State to 25% of current rates by 2020. [1]

The policy is based on results from a task force convened by the New York State Department of Health (DOH) in October 2014 and enacted by Governor Andrew M. Cuomo. [2, 3] the policy is based on three key goals.

- To identifying people with HIV who are not yet diagnosed and to link them to health care.
- To link and retain people in health care who are already diagnosed with HIV, and to increase use of HIV treatment to 85% of people to maximise viral suppression so they remain healthy and prevent further transmission.
- To facilitate access to Pre-Exposure Prophylaxis (PrEP) for people at high risk of HIV to keep them HIV negative.

Last year, 3000 people were diagnosed with HIV in New York, and the target for 2020 is to reduce this to less than 750, representing a reduction of 75%.

The task force included over 70 activists, health service providers, researchers, and public health professionals and met intensively over the past four months, reviewing over 300 recommendations.

Meeting proceedings are webcast [4] and the concluding statements by activist and co-chair Charles King from Housing Works are especially important. [5]

C O M M E N T

It is important that there was political leadership and support for this initiative.

Last month, Public Health England reported over 7000 new diagnoses in the UK last year, the majority of which were related to recent infections.

It is time that UK prevention initiatives also set ambitious and achievable targets for reducing new infections. These absolute goals can be used to evaluate efficacy of these programmes.

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BASIC SCIENCE & CURE RESEARCH

Is HIV weakening over time? Unlikely, and a sense of déjà vu...

Richard Jefferys, TAG

A little over nine years ago I wrote a blog post with the same title of "Is HIV weakening over time?" about a widely publicised paper claiming that HIV had become less virulent. [1]

Although it's grim to be in the position of pouring cold water on optimistic-sounding scenarios, that paper was based on measuring the ability of HIV to replicate using a laboratory test, and other published data raised questions as to whether the test could actually predict differences in disease progression rates. Today, it's déjà vu, because there has been an explosion of very similar media stories positing that HIV is evolving into a "milder form".

Once again, the study prompting the coverage relies primarily on laboratory measurements of HIV replication capacity, despite the fact that a prior publication - by several of the same authors - reports that results from this test do not predict the rate of CD4 T cell decline over time.

The new study, by Rebecca Payne and colleagues from the laboratory of Philip Goulder, was published by PNAS in December 2014. Helpfully, the full text has been made freely available. [2]

Two populations of HIV positive women are compared, from Gaborone, Botswana and Durban, South Africa. The researchers present evidence that in Botswana, where HIV has been circulating for a longer period, there has been greater virus adaptation to immune responses, leading to more escape mutations and a lower replication capacity. HIV replication capacity is compared using samples from 63 study participants in Gaborone and 16 in Durban, with these participants being closely matched for CD4 T cell counts (important because, as the paper reports, HIV replication capacity in a given individual increases as CD4 T cell counts decline). The average result of the replication capacity test was 0.72 in Gaborone and 0.81 in Durban, indicating that the virus in the former population is slightly less fit. The authors create a mathematical model based on these findings suggesting that both immune responses and the increasingly widespread use of antiretroviral therapy may be contributing to a decline in HIV virulence.

The idea that HIV replication capacity can be linked to disease progression rate derives from a documented correlation between the results of the test and both viral load and CD4 T cell count. However, these correlations are based on measurements taken at single timepoints; in other words, cross-sectional analyses. The question of whether measurement of HIV replication capacity can predict subsequent disease progression rate was addressed in a prior study, [3] which evaluated whether there was a correlation with the rate of CD4 T cell decline over time. No such correlation was found, nor even a hint of one. The discussion section of the Journal of Virology paper containing this result states:

"Therefore, although there may be a benefit to decreased replication capacity (as supported by cross-sectional correlations with viral loads and CD4 counts), the data do not support an enduring benefit or a lasting significant impact of Gag-protease replication capacity on the rate of disease progression, at least once the chronic infection stage has been reached... the long-term clinical impact of immune-driven fitness costs requires further investigation, given the evidence for compensation and the observation that replication capacity does not correlate with the subsequent rate of CD4 decline in chronic infection."

It is challenging to try and reconcile this prior result with the claim that the difference in replication capacity found in the new PNAS study would equate to an additional 2.5 years in the average time it takes to progress from HIV infection to AIDS (an estimate offered by Phillip Goulder in the BBC's coverage) [4]. Before concluding that the virulence of HIV is declining, it would be prudent to wait to see if additional studies are able to correlate the apparent differences in HIV replication capacity with differences in CD4 T cell counts and health outcomes over time.

An additional wrinkle is that there are other studies arguing that HIV virulence is *increasing* over time; a meta-analysis with this finding was published in 2012 [5] and a new analysis presented at CROI 2014 (and just published in the December issue of The Lancet HIV) reached the same conclusion.

There might be explanations for these very disparate results, but - pending additional evidence - it seems reasonable to maintain a healthy scepticism about all of them.

Source

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Quantification of latent HIV induction by vorinostat

Gareth Hardy, HIV i-Base

Various compounds are being tested to induce the latent HIV reservoir, enabling its depletion by a combination of virus-induced cytopathic effects and the action of ARVs. Of these, the most studied compounds are histone deacetylase inhibitors (HDACi) such as vorinostat (also known as SAHA).

In patients on ART, vorinostat induces expression of cell-associated HIV RNA in resting memory CD4 T cells, [1]

Despite this, two cautions have recently emerged about the potential efficacy of the current leading HDACi. Firstly, the induction of HIV RNA may not lead to production of viral particles, causing the cytopathic effects that kill infected cells: the so called “kick and kill” strategy. Secondly, it is unclear what proportion of latent proviruses HDACi can reactivate.

Anthony Cillo and colleagues from the University of Pittsburgh, PA, investigated these issues by comparing the ability of vorinostat to induce viral reactivation in vitro with global T cell activation using anti-CD3 antibodies. [2]

While activating T cells through CD3 is the most effective means of reactivating latent HIV, this approach is too toxic for clinical use. In vitro, CD3 activation enables quantitation of the total proportion of proviruses that can produce infectious virions. Cillo et al treated resting CD4 T cells from 13 HIV positive patients who had received ART for an average of 8 years, with either anti-CD3 to induce maximal latency reversal, or with SAHA. Limiting serial dilutions of CD4 T cells were set up to quantify the number of cells from which HIV could be reactivated, either as whole viral particles or cell-associated unspliced HIV RNA. Virus expression was normalised to the number of cells bearing proviral DNA, to calculate the fractional provirus expression (fPVE).

The maximal fPVE was assessed by stimulating CD4 T cells with antibodies to CD3 for 7 days. The fraction of proviruses that could be reactivated by SAHA was determined by culturing CD4 T cells with 0.5 μ M vorinostat for 7 days. Culture with CD3 antibodies led to global T cell activation as >94% of cells expressed CD25 and HLA-DR. Treatment with vorinostat did not result in T cell activation. HIV DNA levels increased by an average of 27-fold in cells treated with CD3 antibodies, suggesting proliferation of infected cells. In cells treated with vorinostat, HIV DNA levels increased two-fold.

Expression of virions in supernatants was detected using the Roche TaqMan assay. Global T cell activation with CD3 antibodies induced virion-associated RNA in an average of 1.5% of CD4 T cells that harboured proviral DNA. Vorinostat induced virion RNA in an average of 0.12% of CD4 T cells that harboured proviral DNA. The average fPVE ratio of vorinostat to anti-CD3 treatment was 0.05, demonstrating that vorinostat induces a fraction of the proviral expression achieved with global T cell activation.

In two patients for whom sufficient cells were available, the proportion of proviruses that could produce cell-associated unspliced HIV RNA were assessed. In response to global T cell activation, 6.8% and 8.2% of proviruses produced unspliced HIV RNA from donors 4 and 5 respectively. This amounted to a 2.4 and 2.0 fold higher induction than seen for production of virions in supernatant.

In contrast, treatment with vorinostat induced unspliced HIV RNA in 0.09% and 0.19% of proviruses, which amounted to a 3.1 and 1.4-fold higher induction than for production virions.

Finally, the relationship between induction of virions and cell-associated unspliced HIV RNA was assessed, in response to vorinostat or global T cell activation. A significant correlation was found between cellular unspliced HIV RNA and virion production when cells were stimulated with anti-CD3 [$\rho = 0.67$, $p < 0.001$]. In contrast there was no relationship between cellular unspliced HIV RNA and virion production in cells treated with vorinostat [$\rho = 0.21$, $p = 0.99$]. The data distribution suggests that a relationship is not observed here because expression of cellular HIV RNA occurs without virion production. This may explain why low-levels of plasma viraemia are not consistently observed in individuals treated with vorinostat, despite three to five fold increases in cell-associated HIV RNA [1].

This data suggests that vorinostat is not a potent inducer of replication competent latent HIV. The question of why expression of cellular unspliced HIV RNA does not correlate with production of virions may have at least two answers.

First of all, mutations will arise in any part of the viral genome, which can disable replication. While unspliced RNA is produced, any of the multiple subsequent steps required for virus assembly could be disabled. Therefore expression of unspliced HIV RNA does not necessarily equate to production of virions. The disassociation between the two is probably overridden in the case of global T cell activation, as a result of maximal viral induction.

The second reason is that there are multiple mechanisms that maintain HIV latency, of which HDACs represent just one. While HDACi may enable expression of unspliced HIV RNA in a proportion of cells capable of producing virus, the remaining steps required for complete viral production may still be regulated by other cellular mechanisms. If this is the case, one solution may be to use HDACi in combination with different latency reversing agents, which act on the other cellular mechanisms, in order to achieve full reactivation of inducible proviruses allowing reservoir depletion to occur.

Despite the disappointing lack of virion production with the current leading HDACi compounds, there is at least one caveat worth considering. The effectiveness of latency reversing agents is assumed to depend on their ability to induce production of virions, causing viral cytopathic effects that kill infected host cells. Studies investigating the efficacy of HDACi have focused on production of virions or HIV RNA. What is not known is whether HDACi can induce expression of viral proteins. If proteins can be induced, infected cells could then become targets for components of the immune response, including cytotoxic T cells and Natural Killer cells.

These cells may need to be induced themselves, by immunotherapy. But the expression of viral proteins should be sufficient to unmask latently infected cells from the immune response. The problem here is that expression of viral proteins is a hard parameter to measure, because no assay for protein detection has the sensitivity to detect the very low frequency of reactivated latently infected cells on a single cell basis. Despite this, one recent study attempted to address this question by assessing expression of multiply spliced HIV RNA that encodes tat and

rev proteins, as well as assessing the induction of new T cell responses to HIV gag as a crude indicator of renewed viral protein expression, in a patients receiving vorinostat with ART. [3]

Unfortunately, there was no evidence for increased expression of multiply spliced HIV RNA, or induction of new HIV-specific T cell responses, providing evidence that vorinostat does not induce viral protein expression. There is therefore mounting evidence that vorinostat on its own is unlikely to be effective in the proposed “kick and kill” strategy to diminish the HIV reservoir.

References

1. Archin NM et al. Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy. 2012. Nature. 15 (8). 482-485.
2. Cillo AR et al. Quantification of HIV-1 latency reversal in resting CD4+ T cells from patients on suppressive antiretroviral therapy. 2014. PNAS. 111(19). 7078-7083.
3. Elliot JH et al. Activation of HIV transcription with short-course Vorinostat in HIV-infected patients on suppressive antiretroviral therapy. PLoS Path. 2014. 10 (11).

ON THE WEB

Online video resources

Aidspans video on gay life and death in Ghana

On 1st December 2015, Aidspan's posted its first documentary on YouTube about growing up gay in Ghana: “I didn't want to bring shame on my family”.

This is short 9 minute video deserves wider viewing. Please watch it and then promote it.

<https://vimeo.com/114014571>

Online articles

Journal of Virus Eradication: New open-access journal

A new open-access online and print journal was launched in December 2014, dedicated to the rapidly developing field of virus eradication. It is particularly interested in publishing original research on HIV, hepatitis viruses, HPV, herpes and flu but work on other viruses is also included.

The first issue is now online:

www.viruseradication.com

Original research will be accepted from all areas covering preventative and therapeutic developments, including vaccines, viral reservoirs and persistence and virus eradication

Scope includes from virology to epidemiology, immunology to pharmacology, pre-clinical, clinical and in vitro research , ethical and social questions.

There is no charge for authors to publish original research.

Community reports

RITA: HIV and kidney disease

The latest issue of RITA, focused on kidney disease in people with HIV.

<http://centerforaids.org/pdfs/1114rita.pdf>,

This issue includes three review articles and an interview with Christina Wyatt, a top HIV/kidney expert.

Dr. Wyatt offers insights on screening HIV-positive people for kidney disease, referring them to nephrologists, and using TDF. She frankly weighs prospects for TAF, the next-generation tenofovir that may have fewer renal and bone side effects.

The three review articles analyse research on kidney disease prevalence in people with HIV, kidney disease as a cardiovascular risk factor, classic and HIV-specific risk factors for chronic kidney disease, and CKD screening and monitoring in people with HIV.

FUTURE MEETINGS

Conference listing 2015

The following listing covers some of the most important upcoming HIV-related meetings and workshops. Registration details, including for community and community press are included on the relevant websites.

XXIV International HIV Drug Resistance Workshop

21-22 February 2015, Seattle, Washington

<http://www.informedhorizons.com/resistance2015>

5th International Workshop on HIV & Women, from Adolescence through Menopause

21-22 February 2015, Seattle, Washington

<http://www.virology-education.com>

22nd Conference on Retroviruses and Opportunistic Infections (CROI 2015)

23-26 February 2015, Seattle, Washington

<http://www.croi2014.org>

21st BHIVA Spring Conference

21 - 24 April 2015, Brighton, UK

<http://www.bhiva.org/AnnualConference2015.aspx>

Towards an HIV Cure Symposium

18 - 19 July 2015, Vancouver, British Columbia, Canada

<http://hivcure.ias2015.org>

8th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2015)

19 - 22 July 2015, Vancouver, British Columbia, Canada

<http://www.ias2015.org>

17th International Workshop on Co-morbidities and Adverse Drug Reactions

Date and venue TBC, but linked to EACS in Barcelona

<http://www.intmedpress.com/comorbidities/default.cfm>

15th European AIDS Conference (EACS)

21-24 October 2015, Barcelona

<http://www.eacs-conference2015.com>

7th International Workshop on HIV Persistence During Therapy

8-11 December 2015, Miami

<http://www.hiv-persistence.com>

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website: updates for PDA access

The i-Base website is designed to meet access standards for PDA, iPad, tablet, Windows 8 and touch screen access.

It is now faster and easier to access, use and navigate.

<http://www.i-Base.info>

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

RSS news feed is available for HIV Treatment Bulletin for web and PDA.

An average of 200,000 pages from individual ISP accounts contact the website each month, with over 6000 hits a day.

Non-technical treatment guides

i-Base treatment guides

i-Base produce six booklets that comprehensively cover five 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>

- NEW: Introduction to combination therapy (July 2014)
- HIV testing and risks of sexual transmission (February 2013)
- HIV and quality of life: side effects & complications (July 2012)
- Guide to changing treatment and drug resistance (February 2013)
- Guide to HIV, pregnancy & women's health (March 2013)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (November 2013)

Publications and reports

HIV Treatment Bulletin (HTB)

This is the journal you are reading now: a review of the latest research and other news in the field. HTB is published every two months in print, PDF and online editions.

HTB South

A quarterly bulletin based on HTB but with additional articles relevant to Southern Africa. HTB South is distributed in print format by the Southern African HIV Clinicians Society (www.sahivsoc.org) to over 20,000 doctors and healthcare workers. It is also available as a PDF file and is posted online to the i-Base website.

HTB Turkey

HIV Tedavi Bülteni Türkiye (HTB Turkey) is a Turkish-language publication based on HTB.

HTB West Balkans

HIV Bilten is an edition of HTB in Bosnian, Montenegrin, Croatian and Serbian, for the West Balkans, produced by Q Club.

Why we must provide HIV treatment information

Text from activists from 25 countries and 50 colour photographs by Wolfgang Tillmans.

Translations of i-Base publications

Original material published by i-Base can be translated and reprinted, and has so far been produced in over 35 languages. Information to support this is available on the i-Base website.

<http://i-base.info/category/translations>

Advocacy resources

Online treatment training for advocates

<http://i-base.info/ttfa>

Entry-level curriculum relating to HIV and treatment.

Eight modules include: immune system and CD4 count; virology, HIV and viral load; an introduction to antiretrovirals (ARVs); side effects of ARVs; opportunistic infections and coinfections: HIV and pregnancy; drug users and HIV; and clinical trial design and the role of advocates

UK CAB: reports and presentations

The UK Community Advisory Board (UK CAB) is a network for community advocates from across the UK that has been meeting since 2002. It now includes over 580 members from over 120 organisations.

<http://www.ukcab.net>

Phoneline and information services

Online Q&A service

An online question and answer service that now has over 3000 questions and comments online. Questions can be answered privately, or with permission, can be answered online.

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

Order publications and subscribe by post, fax or 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>

htb(e)

HIV TREATMENT BULLETIN (e)

HTB(e) is the electronic version of HTB, which is published six times a year by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered by fax or post using the form on the back page or directly from the i-Base website:

<http://www.i-Base.info>

by sending an email to: subscriptions@i-Base.org.uk

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1 5 10 25 50 Other _____

• Guide To HIV and hepatitis C coinfection (November 2013)
1 5 10 25 50 Other _____

• Clinical Trials: a community guide to HIV research (March 2009)
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Treatment guides in other languages are available as PDF files on the website

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