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HIV/AIDS TOWARDS AN AIDS-FREE GENERATION

CONTENT

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TOWARDS AN AIDS-FREE GENERATION

The first hint that a new disease was killing people came in 1981. What followed were decades of tragedy. During those years, the world was still woefully short of scientific understanding of all aspects of the disease. All people infected with the Human immunodeficiency virus (HIV) were certain of dying of acquired immunodeficiency syndrome (AIDS) or AIDS related conditions, sooner or later. Treatment was limited to treating opportunistic infections and AIDS related malignancies, but with major difficulties in diagnosis and treatment. When the first anti-retroviral drugs became available in 1987, they had little effect. It took 15 years to discover more powerful antiretroviral drugs, with acceptable side-effects; when given in a combination of three active ingredients they can suppress all the different mutations that occur in the complex virus. Antiretroviral therapy (ART) with three drugs (triple therapy)was widely initiated and it gradually became possible for people with HIV to live a normal live with a chronic condition.

To date, tremendous progress has been made. But many challenges remain, and HIV continues to be a major global public health issue. In 2017, an estimated 36.9 million people were living with HIV, the vast majority (66%) living in sub-Saharan Africa. That same year, 940,000 people died of AIDS-related conditions, which is about half the number that died since the peak in 2004 (1.9 million).

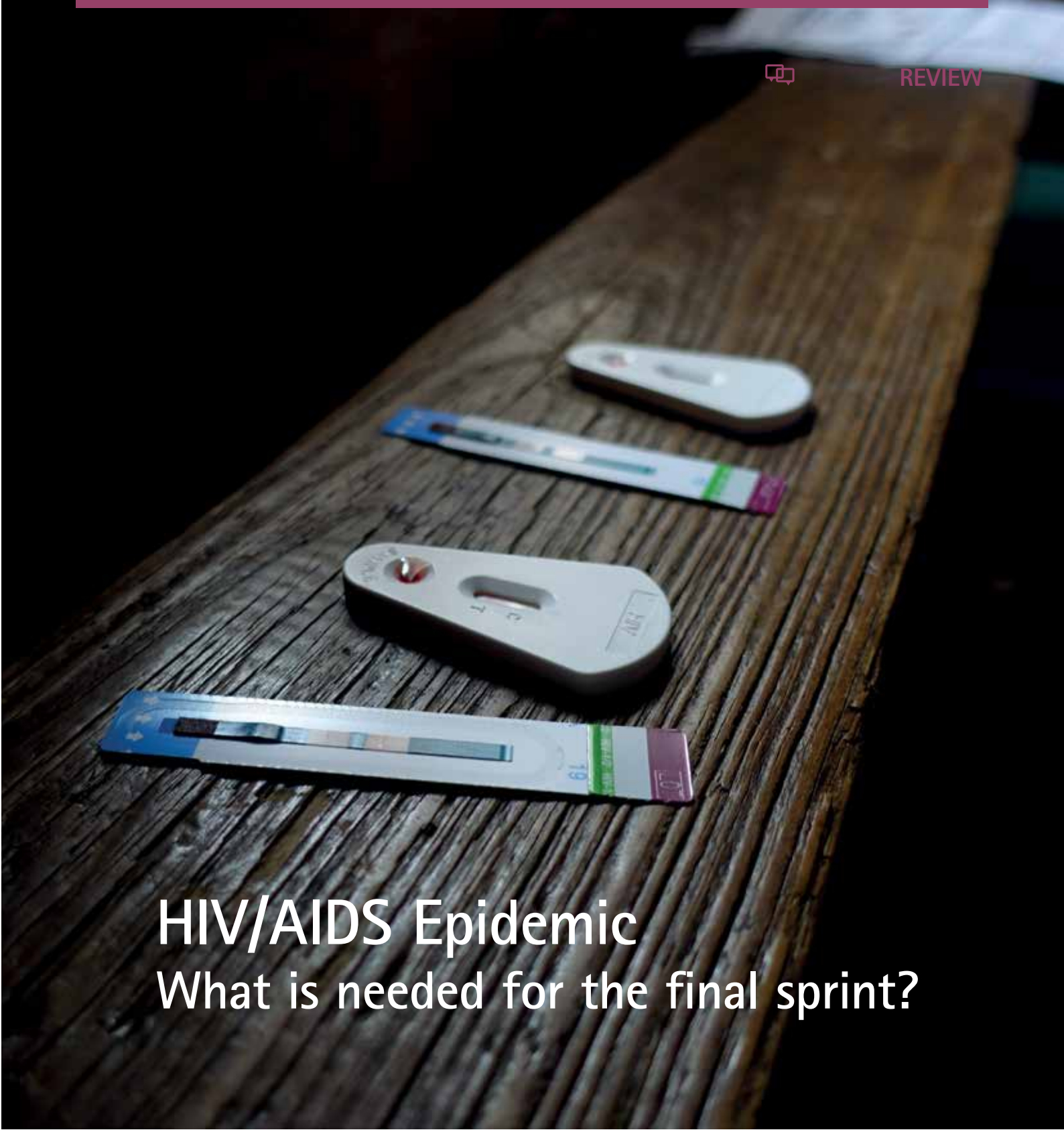
National governments, international organizations and aid agencies keep fighting to stop the HIV/AIDS epidemic. UNAIDS stated that 'it will be impossible to end the epidemic without bringing HIV treatment to all who need it'. In particular the roll-out of ART in Africa, which started in 2004, was a major challenge. In 2014, UNAIDS set the ambitious '90-90-90: treatment for all' targets: 'by 2020, 90% of all people living with HIV would know their HIV status; 90% of all people with diagnosed HIV infection would receive sustained antiretroviral therapy; and 90% of all people receiving antiretroviral therapy would have achieved viral suppression'. In sub-Sahara African countries, national programmes adopted the 90-90-90 targets to improve HIV healthcare. Two articles in this edition highlight experiences and challenges in Lesotho and Malawi, two countries with a high burden of disease.

Similar to other viral infectious diseases, such as smallpox, poliomyelitis or infection with Ebola virus, also in HIV infection there are people who survive the infection, even without treatment. But there has never been a documented case of someone infected with HIV who cleared the virus. And why is there not yet a vaccine for HIV, like for other infectious diseases, or a prophylactic drug? Two articles in this edition focus on prevention of HIV. One discusses the bumpy road towards the development of an HIV vaccine, the other pre-exposure prophylaxis, which has turned out to be highly effective.

Globally, an estimated 1.8 million children are living with HIV. Children in particular are extremely vulnerable to HIV related diseases. Fortunately, over the past years, access to ART for children has increased considerably. How is it possible that only about 52% of the children actually receive medication? Two articles focus on challenges in the treatment of children and their approach for improvement. The column in this edition is about stigma and discrimination, which people with HIV often face from the moment they are diagnosed.

We do not know yet when an AIDS-free generation will become a reality. To date, already much improvement has been achieved. However, the fight against HIV/AIDS continues. It is our obligation to the 39 million people worldwide who have died from AIDS.

Andrea van Meurs, Ed Zijlstra



HIV/AIDS Epidemic
What is needed for the final sprint?

HIV tests

UNAIDS 90–90–90 TARGETS – MISSION IMPOSSIBLE?

Antiretroviral therapy (ART) programs focusing on the prevention of mother-to-child HIV transmission are the cornerstone of a remarkable success in scaling up ART globally. It is estimated that, since 2000, two million HIV infections in children have been averted thanks to ART programs.[1] Recent data indicate that AIDS-related mortality has declined by 34% since 2010 – again largely driven by the steady scale-up of ART.[2] However, we are still far from achieving the targets for 2020 set by the joint United Nations programme on HIV/AIDS (UNAIDS), called the '90-90-90 targets'.[2] The first target is to ensure that 90% of all people living with HIV are aware of their status. The second target is that 90% of those diagnosed receive sustained ART. And the third target means that 90% of those receiving ART have viral suppression. Mathematical models suggest that if we achieve the UNAIDS targets by 2020, a reduction of the global HIV incidence

from the current level of 2 million to a level of 500,000 could be expected in 2020, and subsequently the end of the epidemic by 2030. These models are based on scientific evidence that, irrespective of the disease stage (i.e. CD4 count), ART initiation not only has individual therapeutic benefits but also prevents onwards HIV transmission. It is therefore strongly endorsed by WHO.[3-5]

This 'Treatment for All' strategy not only poses financial and human resource challenges, but also means that more asymptomatic patients will enter the HIV care cascade for whom the benefit of ART might not be evident, and who might therefore be less motivated to attend their nearest clinic for ART initiation and subsequent drug refills. Thus, the second UNAIDS target is often referred to as the Achilles heel of the 90-90-90 strategy.[6] In the case of community- or home-based HIV testing in sub-Saharan Africa, overall linkage to care rates after a positive HIV test are below 50% in the vast majority of studies.[7]

SAME-DAY ART INITIATION – A SIMPLE WAY FORWARD?

The RapIT trial by Rosen and colleagues in 2016 demonstrated a possible innovative approach to deal with this Achilles heel: same-day ART initiation.[8] Subsequently, in 2017, WHO expanded the guidelines on ART initiation to focus on rapid initiation.[9] The RapIT trial, however, was conducted in a clinic-based setting and still used CD4 for ART initiation criteria.

The first study to assess the effect of same-day ART initiation in the community – regardless of CD4 count – was the CASCADE study by our research group, published in the Journal of the American Medical Association.[10] This parallel-arm, open-label randomized clinical trial was conducted in Lesotho, which has the second-highest adult HIV prevalence globally (25.6%). More than 70% of Lesotho's population lives in rural areas, which negatively affects engagement in care after home-based HIV testing.[11] Almost 300 adults from rural and urban areas, who tested positive for HIV during a home-based testing campaign and never received ART, were randomized to either receive the offer of same-day ART initiation on the spot or the usual referral to a nearby health facility. In the same-day initiation group, the nurse performed a clinical assessment, point-of-care baseline blood tests (CD4, creatinine, and haemoglobin), counselling, and a readiness assessment. If the patient agreed to being part of the study and was ready to start ART, a one-month supply of the standard first-line ART was dispensed. 97.8% of the patients in the same-day ART offer group were ready to start treatment the same day. The primary outcome measures were linkage to care at 3 months and viral suppression at 12 months. A significant improvement in 3-month linkage to care was observed (68.6% in the same-day group vs 43.1% in the usual care group, p<0.001) and, more importantly, higher rates of viral suppression at 12 months after enrolment (50.4% in the same-day group vs 34.3% in the usual care group, p=0.007), which indicates successful engagement in care.[10]

These results demonstrate the feasibility and effectiveness of same-day ART initiation in the community. Moreover, it shows that a simple intervention that lowers the first barrier in the HIV care cascade (linking after testing) can have a huge impact along the entire cascade until viral suppression.

A limitation of this study is that it excluded pregnant, breastfeeding women, those with advanced HIV disease, and people with active tuberculosis or other chronic conditions – groups that may benefit the most from rapid ART initiation. Furthermore, overall virologic suppression rates were still below the UNAIDS 90-90-90 targets, highlighting the need for enhanced and sustained efforts to engage people in care.

VIBRA MODEL – ADDRESSING THE SHORTCOMINGS OF SAME-DAY ART INITIATION

Our response to the challenges of sustained engagement in care after ART initiation in the community is called VIBRA (Village-Based Refill of ART), an innovative ART delivery model.

Point-of-care HIV testing from door to door in rural Lesotho.

There is increasing global consensus that new ART delivery models are needed, especially in rural settings that face shortages of doctors and nurses and limited financial resources.[12] These models should not only increase engagement in care but also be cost-effective without compromising quality of care, and have the potential to be replicated in similar settings. One promising approach is to further decentralize ART services and shift tasks to lay health personnel, i.e. drug adherence monitoring, TB screening, and psychosocial support in the community. WHO thus endorses the training of community health workers as a decentralization strategy, and UNAIDS launched a recruitment plan for 2 million community health workers in Africa.[13,14] Most countries in sub-Saharan Africa have some form of a community health worker program in place. A long-standing public sector cadre of lay health personnel, called village health workers (VHW), was introduced in 1978 in Lesotho with more than 4000 VHWs currently successfully operating in all districts. VHWs are members of and appointed by the community to provide a package of basic services at the household level, although they have no formal professional health education. They are elected by the village members, complete a 2-weeks training followed by periodic refresher courses, and are supported and supervised by staff from nearby health centres. They receive a monthly stipend of USD 20 from the Ministry of Health. VWH's tasks are mostly preventive and include the promotion of antenatal care, education about hygiene, sanitation, nutrition, HIV testing and counselling, the referral of sick people to the health centre or hospital, the organization of community meetings, and tracing patients who are lost to follow-up. Specifically, regarding HIV service delivery, it has been shown that VHWs play a pivotal role in reducing stigma and discrimination.[15]

In close collaboration with a Swiss-based but locally long-standing active non-profit organization (SolidarMed) and other local stakeholders, we designed the VIBRA model, a differentiated ART delivery model that builds on the VHW program and uses SMS technology, addressing the challenge of long-term treatment adherence after same-day home-based ART initiation. Currently, we are running a large cluster-randomized trial in two districts of Lesotho in order to assess the VIBRA model. People living with HIV, who we find during a home-based testing campaign in rural villages, are offered ART initiation at home as performed in the CASCADE trial. In the intervention clusters, the newly initiated patients have the option of going to their VHW for ART visits and drug refills and to visit the health facility only once or twice per year for clinical follow-up and blood testing. Additionally, they receive automatically generated SMS messages, sent through a secured online platform. The platform is connected to the governmental district laboratory database with access to viral load results from all study districts. Apart from periodic standard treatment reminders (without explicitly mentioning HIV or HIV care), they may also receive personalised messages, depending on their viral load level. Patients with high viral load levels are asked to revisit the health facility as soon as possible in order to assess adherence to treatment, whereas patients with suppressed viral load levels can stick to their prolonged follow-up refill visit. (Study protocol in publication status. Project homepage: https://getonproject.wordpress.com/)

CONCLUSION

Effective, innovative and differentiated strategies are needed to improve the HIV care cascade, especially in rural settings. Same-day ART initiation and the VIBRA model will probably not be the magical solution to reach the UNAIDS targets globally, but they may be an important piece in solving the complex puzzle of scaling up ART programs. First results are expected by the end of 2019.

The views expressed in this article are solely those of the author and do not necessarily reflect those of his associated institutions (Swiss TPH / SolidarMed).

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Our research in Lesotho: www.swisstph.ch/en/projects/hiv-care-research-in-lesotho

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THERE IS INCREASING GLOBAL CONSENSUS THAT NEW ART DELIVERY MODELS ARE NEEDED, ESPECIALLY IN RURAL SETTINGS THAT FACE SHORTAGES OF DOCTORS AND NURSES AND LIMITED FINANCIAL RESOURCES

Campaign team, including material for same-day ART initiation such as the point-of-care CD4 machine.

The bumpy road towards an HIV-1 vaccine

An effective HIV vaccine is still not available, even though almost 40 years have passed since the detection of the virus. Two major HIV types exist, HIV-1 and HIV-2, with the former being the more widespread and pathogenic one. The major challenge for an effective HIV-1 vaccine is its enormous viral diversity. Vaccine-induced immune response will have to be able to cope with this diversity in order to be broadly protective against circulating HIV-1 strains.
While most licensed antiviral vaccines consist of live-attenuated or inactivated forms of the pathogens, these approaches are deemed unsafe for HIV-1, as an attenuated form of the virus could revert back to a pathogenic form and inactivation would need to be extremely effective to ensure safety. Therefore, newer vaccine platforms such as protein subunit, DNA, or recombinant viral vector vaccines have been explored. Many vaccine approaches target components of the envelope spike that mediates viral entry into target cells. As the envelope spike is the only viral protein on the outside of the virus, it is the only protein relevant for the induction of neutralizing antibodies, i.e. antibodies that can inactivate the virus (Figure 1). Of over 200 HIV-1 vaccines that have been tested in phase I trials in humans, only a handful progressed to phase IIb and III clinical trials, and none have been a great success. [1] However, several breakthroughs in the fundamental understanding of HIV-1 biology and immunology have driven new directions in HIV-1 vaccine research with promising results in preclinical studies. In this article, we describe the bumpy research path towards the development of an HIV-1 vaccine.

EARLY FAILURES (1998 – EARLY 2000S)

The initial focus of HIV-1 vaccine research was on inducing humoral immunity via antibodies. Two phase III trials, VAX004 and VAX003 that started in 1998 and 1999, in the US and Thailand respectively, were designed to induce neutralizing antibody responses. Both studies tested a recombinant gp120 protein, one of the subunits of the HIV-1 envelope spike (Figure 1). Both vaccines failed to induce neutralizing antibodies and showed no reduction in the percentage of individuals that acquired HIV-1 over time compared to placebo recipients.[1]

After the failure of these antibody-focused vaccines, the attention shifted to cellular immunity via T cells. Two trials, the STEP and Phambili trials, tested a vaccine consisting of a weakened recombinant form of a common cold virus, adenovirus type 5, expressing internal viral proteins to induce T-cell responses (Figure 1A). This vaccine also did not provide protection, and the trials were stopped prematurely because the vaccine was suspected to increase the risk of HIV-1 infection.[1]
A third trial to test the T cell concept, HVTN505, used a vaccine that contained DNA plasmids encoding internal viral proteins and gp120 proteins. Similar to the previous studies, it did not show any efficacy against HIV-1 acquisition.[1]

A MODERATE SUCCESS AND LESSONS LEARNED (2009 – NOW)

While the above vaccines aimed to induce either humoral or cellular immunity, simply combining such vaccines led to the first success, albeit a very modest one. The famous RV144 trail, conducted in Thailand, remains the only HIV-1 vaccine trial to demonstrate efficacy against HIV-1 acquisition. The trial evaluated a prime-boost vaccine that was composed of a recombinant non-replicating canary pox vector encoding internal viral proteins, followed by a gp120 protein boost (Figure 1). The study showed an efficacy of 31% protection against HIV-1 acquisition and raised hopes that generating a successful HIV-1 vaccine might be feasible.[2] To improve the quality, quantity and durability of the antibodies associated with the protection observed in the RV144 trial, a follow-up phase IIb trial, HVTN702, is currently being conducted in South Africa using geographically matched vaccine components.[3] A second phase IIb trial in sub-Saharan Africa, Imbokodo/HVTN705, also builds on the RV144 results and uses a recombinant adenovirus type 26 virus expressing immunologically optimized internal and envelope proteins, followed by booster immunizations with a geographically matched envelope protein.[4]

AIMING FOR BROADLY NEUTRALIZING ANTIBODIES

None of the above vaccines induce neutralizing antibodies against circulating virus strains – which is how most licensed viral vaccines work – let alone broadly neutralizing antibodies, i.e. antibodies that can neutralize diverse virus strains. This is a significant shortcoming, especially considering that passive immunization of monkeys with broadly neutralizing antibodies provides strong protection from virus acquisition.[5] Such broadly neutralizing antibodies do develop in approximately 20-30% of HIV-1 infected patients and some are able to neutralize more than 90% of the highly diverse circulating HIV-1 strains. This demonstrates that the human immune system can make such antibodies. Four complementary and exciting new routes aimed at inducing broadly neutralizing antibodies will be put to test in early phase clinical studies in 2018-2020.

SOLUBLE ENVELOPE SPIKE VACCINES

The failure of previous HIV-1 vaccines is partly attributable to the fact that they only used a component of the envelope glycoprotein spike, monomeric gp120 or a misfolded version of it (Figure 1B). The gp120 subunit lacks a number of neutralizing antibody epitopes and also exposes immuno-dominant epitopes that serve as immune decoys. Over the last five years, significant progress has been made in generating better mimetics of the native envelope spike and the prototype mimetic is the BG505 SOSIP trimer. This stabilized envelope protein was the first to induce strong neutral-

izing antibody responses in animal vaccination studies, albeit only against the sequence-matched virus [6], and it will be evaluated in a phase I trial in 2019.

LINEAGE ENVELOPE VACCINES

The broadly neutralizing antibodies in HIV-1 infected patients do not develop instantly in response to the incoming virus. Rather they usually emerge many years after the initial infection and are probably the product of continuous co-evolution of the immune-escaping viruses.[7] It is therefore unlikely that such antibodies will develop in response to any vaccine with a constant composition. The evolution of the broadly neutralizing antibody response has been extremely well documented in a patient named 'CH505' and revealed the underlying mechanisms between viral escape and antibody maturation. To recapitulate the co-evolutionary process that led to the development of broadly neutralizing antibodies in patient CH505, envelope vaccines based on the evolving viruses in that patient have been generated and a phase I clinical trial with sequential immunizations with these vaccines is now in progress.[7]

ACTIVATING B-CELL PRECURSORS OF BROADLY NEUTRALIZING ANTIBODIES

Sequential immunization may be necessary for antibodies to become broadly neutralizing antibodies, but an important step in such a strategy is for the first immunization to select for B-cells that have the intrinsic capacity to generate broadly neutralizing antibodies.[7] However, current envelope vaccines generally do not engage these desirable B-cells, so specifically engineered vaccines are needed. The most advanced vaccine candidate to achieve this is eOD-GT8.[7] A phase I trial has recently been started to test whether eOD-GT8 can select and activate the right precursor B cells in humans. A second vaccine designed to activate such B-cells is based on the BG505 SOSIP trimer and will enter human trials in 2019.[8]

EPITOPE-FOCUSED ENVELOPE VACCINES

Envelope vaccines often display many potential distracting epitopes. Vaccines that are designed to focus the immune system on a particular epitope might resolve this problem and activate the desirable B-cells. An attractive candidate for epitope focusing is the envelope fusion peptide, as it is a relatively simple epitope. Vaccination of mice and monkeys using a fusion peptide vaccine, followed by a BG505 SOSIP trimer vaccine, resulted in the induction of neutralizing antibodies.[7] A human clinical trial following this concept is scheduled to start in 2019.

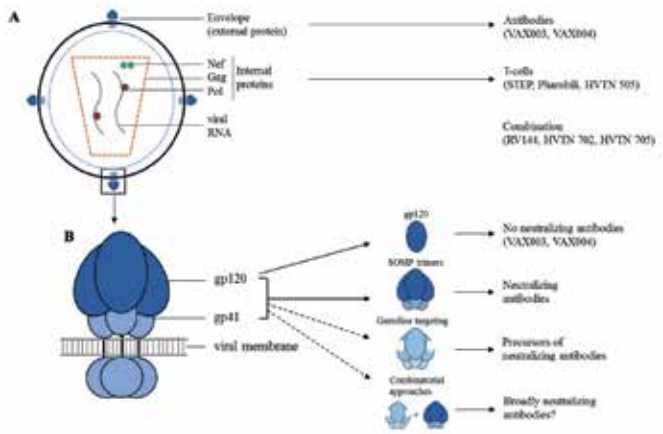

Figure 1: Schematic overview of the HIV-1 envelope glycoprotein trimer and vaccine candidates.

A. The HIV-1 particle. Indicated are the different viral proteins that have been used in different clinical trials.

B. The HIV-1 envelope glycoprotein trimer anchored in the cell membrane. Indicated are the gp120 and gp41 subunits, the monomeric gp120 vaccine candidate, the soluble cleaved native-like SOSIP.664 envelope trimer and the germline targeting trimer.

CONCLUDING REMARKS

Ideally, an HIV-1 vaccine should induce high titres of broadly neutralizing antibodies to protect against virus infection, but no vaccine candidate is currently able to do so. Different approaches are being pursued in order to achieve this goal, with promising results in preclinical studies. A very promising approach involves targeted activation of desirable precursor B-cells of broadly neutralizing antibodies, a necessary first step. Furthermore, the SOSIP trimers are able to induce neutralizing antibodies in preclinical studies. None of the four strategies described above are mutually exclusive, and when used in combination they are likely to be employed more successfully (Figure 1B). After years of exploring the effectiveness of these separate approaches, there is hope that combining them will provide an effective protective HIV-1 vaccine.

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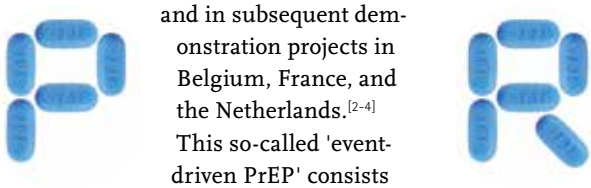
New tools for HIV prevention: pre-exposure prevention

Before HIV treatment was available, prevention focused on ABC: 'Abstinence, Be Faithful, or use Condoms'. This paradigm had its limitations, and HIV prevention programmes have since refocused their strategies. There is greater recognition of the heterogeneity of the epidemic in sub-Saharan Africa and among various vulnerable 'key populations' around the world. New prevention strategies include voluntary medical male circumcision (VMMC) and 'treatment-as-prevention' (TAP). Unfortunately, an effective vaccine, the holy grail of HIV prevention, is not yet on the horizon.
Pre-exposure prophylaxis, or PrEP, is a new and highly effective prevention method. In this article, we will discuss what PrEP is, what its efficacy and effectiveness is, and how trials and demonstration studies impact PrEP provision. We also share some prospects of PrEP provision in sub-Saharan Africa (sSA).



WHAT IS PrEP?

Pre-exposure prophylaxis entails taking anti-microbial or antiviral drugs before the exposure to the microbe or virus has occurred. Prophylaxis against malaria with antimalarials is the best known example of this approach. For HIV, the concept dates back at least 15 years, when animal experiments with a new generation of antiretroviral medicines suggested that new antiretroviral medicines could prevent HIV acquisition.

PrEP can be topical or systemic. Vaginal microbicides, to be applied prior to sexual intercourse, are a topical form of PrEP. Various topical products have been examined in phase 2 and phase 3 studies. By and large, these products have been disappointing. Some did not work at all, while others did work but adherence was low. Topical products are presently not rolled out as public health interventions.

Systemic PrEP is the oral or intramuscular administration of antiretrovirals (ARV). So far, only one ARV combination has been registered for use as PrEP: Emtricitabine/Tenofovir Disoproxil (FTC/TDF).

Oral PrEP can be taken on a daily basis (daily one tablet FTC 200 mg/TDF 245 mg), or on an on-demand basis. This latter option was demonstrated to be highly efficacious in one RCT [1] and in subsequent demonstration projects in Belgium, France, and the Netherlands.[2-4] This so-called 'event-driven PrEP' consists of two tablets of FTC/TDF between 2 and 24 hours prior to sex, and one tablet daily after sex for two days. If a person has sex on subsequent days, taking a daily dose continues until he or she has taken PrEP for two days following the last sex act. A phase 1 trial of intermittent dosing in men who have sex with men (MSM) conducted in Kenya in 2009-2010 showed that adherence to coitally-dependent doses may be more difficult than adherence to daily dosing. In a qualitative assessment, social impacts such as stigma, rumours, and relationship difficulties due to being perceived as HIV positive were prevalent, and adherence was challenged by complexities of daily life.[5]

WHAT IS THE EFFICACY/ EFFECTIVENESS OF PrEP?

In the various efficacy trials conducted over the past 10 years, HIV protection was directly proportional to adherence in the trial population. The first trial (iPREX), conducted among MSM and transgender women, showed a promising protective efficacy of 46%.[6]

Some have postulated that the tissue levels of the drugs after oral administration are lower in the lower female genital tract than in the anorectal area, and that this might partly explain some of the reduced efficacy in women. Nevertheless, currently recommended dosing regimens are the same for men and women.

In studies with good data, almost all cases of incident HIV infections could be attributed to one of three reasons: (1) acute HIV infection at time of PrEP initiation, which was not detected by HIV tests at baseline; (2) low adherence; (3) stopping taking PrEP. In fact, the occurrence of an HIV infection in an adherent PrEP user is a rare event, and documented cases attract considerable attention.[7] Accordingly, current thinking is that efficacy is nearly 100% if PrEP is adhered to; break-through infections are due to non-adherence or pre-existing drug resistance, and not to an inherent lack of efficacy of FTC/TDF.

FROM EFFICACY TRIALS TO DEMONSTRATION STUDIES TO PrEP ROLL OUT

A total of 98 demonstration studies, including 41 in sSA, are being conducted or completed.[8] These studies provide a strong impetus to PrEP roll-out in HIV prevention programmes. The World Health Organization (WHO) has issued guidelines on the use of PrEP.[9] The WHO recommends the use of PrEP in populations 'at substantial risk of HIV'. Substantial risk was initially defined as populations with an HIV incidence of ≥3% (i.e. 3 infections in 100 HIV-negative people followed for a year). However, how to assess if a person belongs to a population with

PrEP IS AN IMPORTANT NEW PREVENTION METHOD THAT SHOWS GREAT PROMISE FOR IMPACTING THE COURSE OF THE HIV EPIDEMIC IN BOTH LOW- AND HIGH-INCOME COUNTRIES

a substantial risk of HIV infection is a challenge. The Kenya PrEP programme illustrates this. It is providing PrEP free of charge and targets individuals who report any of the following: a sexual partner who is HIV positive or has unknown HIV status, transactional sex, a recent sexually transmitted infection (STI), recurrent use of post-exposure prophylaxis, having sex while under the influence of alcohol, inconsistent condom use, and injection drug use with shared needles and syringes.[10] Many individuals in Kenya who meet one or more of these criteria may have some risk of acquiring HIV, but should they take daily PrEP for sustained periods of time? Notably, current PrEP guidelines in Kenya do not specifically target known risk factors for HIV acquisition among MSM, including anal intercourse without the use of condoms and group sex, although Kenya has large populations of MSM.[11]

PROSPECTS FOR PrEP USE IN SUB-SAHARAN AFRICA

Currently, PrEP programmes in sSA focus mostly on adolescent girls and young women (AGYW) and individuals in sero-discordant couples. Regarding the latter group: the partner newly diagnosed with HIV should start ART immediately, but as it may take up to 6 months before he or she is virally suppressed, the negative partner should be offered PrEP as a 'bridge' (i.e. for 6 months) until the HIV-infected partner is no longer infectious. To facilitate uptake of PrEP among AGYW, three key issues need to be addressed: create demand for PrEP, ensure supply of PrEP, and support adherence to PrEP.[12]

PrEP AND DRUG-RESISTANCE

If a person who is taking PrEP is exposed to an HIV strain that is resistant to either FTC or TDF or both, PrEP may not be effective. As resistance is not an all-or-nothing phenomenon, PrEP effectiveness may simply be reduced in such instances.

Initially, many in the HIV field were concerned that PrEP might lead to drug-resistance and therefore severely undercut therapeutic options in users and non-users alike. The roll-out of PrEP is still limited, and empirical data are not available to either prove or disprove this possibility. However, mathematical model studies have quite convincingly shown that it is highly unlikely that PrEP would lead to substantial additional drug-resistance in a population.[13,14]

PrEP AND CONDOMS

The efficacy of oral PrEP against HIV is very high, and for those who have good adherence to PrEP the risk of acquiring HIV is very low. So if the aim is only to prevent HIV, condoms may not be needed to supplement PrEP. Unfortunately, other STIs like syphilis, gonorrhoea, herpes simplex disease, HPV and chlamydia are not prevented by PrEP.

PrEP use may lead to reduced condom use [15] and thus indirectly lead to an increase in other STIs. This is clearly an undesirable side-effect of PrEP roll-out. In high-income countries with good testing facilities and enough funding for regular monitoring of PrEP users, testing for other STIs is part of such monitoring. In such programs, increased frequency of testing for STIs leads to increased detection and treatment of STIs, and may actually lead to a reduction in the incidence of STIs.[16] This may not be feasible in lower-income countries in view of the high costs of testing for gonorrhoea and chlamydia.

NEW DEVELOPMENTS

A large multicentre, multinational randomised controlled trial (DISCOVER trail) is underway to compare the efficacy of a new antiretroviral, Tenofovir Alafenamide (TAF), combined with Emtricitabine, against the use of FTC/TDF.[17] TAF is already being used for the treatment of established HIV infection. It is as effective as TDF but at only 1/10 of the dose. As TDF has renal and bone side-effects, TAF may be preferable for HIV patients who suffer or may suffer from such side effects. As PrEP is given to healthy individuals, the safety of the drugs may be even more important, and fewer side effects make TAF/FTC an attractive alternative to FTC/TDF. However, this has serious cost implications. The combination FTC/TDF is no longer on patent, and the current price for 30 tablets of FTC/TDF in the Netherlands is around €50; the current cost of 30 tablets of FTC/TAF is €533.

Another promising development is intramuscular administration of PrEP, or subcutaneous depots through a rod. This could be an attractive alternative for those who find daily tablet taking a challenge, or for those who do not want to be seen by household members or intimate partners taking tablets that are also used for HIV treatment.

CONCLUSIONS

PrEP is an important new prevention method that shows great promise for impacting the course of the HIV epidemic in both low- and high-income countries. Among the general population in sSA, there is a clear role for PrEP initiation in sero-discordant

PHOTO:SHUTTERSTOCK

couples. However, as large numbers of new HIV infections will occur among vulnerable populations, including young girls and adolescent women as well as MSM and Transgender women, many of whom are often not engaged in current prevention programmes, the effects of PrEP may be limited in these groups in sSA. PrEP could potentially lead to a reduction in the use of condoms and an increase in the incidence and prevalence of other STIs.

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Advanced HIV disease still prevalent in Malawi despite successful national HIV programme

The Malawi HIV programme is considered a model for the public health approach to antiretroviral therapy (ART) in sub-Saharan Africa. It demonstrates that with government backing, support from (inter)national non-governmental stakeholders and adequate multilateral funding, the prognosis for people living with HIV can be improved dramatically. Mother-to-child transmission can be reduced to below 5% and HIV incidence can be reduced, despite severe socio-economic challenges and a health care system lacking sufficient trained staff.[1] This article presents some examples of successes and several challenges.

EXAMPLES OF MALAWI'S SUCCESSFUL PUBLIC HEALTH APPROACH TO ART

In 2011, Malawi developed its own Option B+ strategy for the prevention of mother-to-child HIV transmission (PMTCT). Pregnant and breastfeeding women who test positive for HIV start their lifelong ART on the very same day (see text box on PMTCT options). This happens irrespective of their clinical condition and CD4 count.[2] This strategy was initially criticized, as there was no evidence of its effectiveness and due to ethical concerns about coercing women to start ART.[3] The Option B+ strategy led to a tremendous increase in access to PMTCT in Malawi. A national study has shown that over a period of seven years, mother-to-child HIV transmission was reduced to levels close to those seen in affluent settings.[4, 5] The Option B+ strategy has now become the preferred WHO policy for resource limited settings.

In 2016, in line with the new WHO treatment guidelines, the Malawi Government introduced universal ART eligibility for all people living with HIV, irrespective of their CD4 cell count and clinical stage of HIV disease. At present, the Malawi HIV programme is close to reaching the ambitious '90-90-90' UNAIDS treatment targets that aim to end the AIDS epidemic: 90% of people living with HIV (PLHIV) know their HIV status, 90% of diagnosed PLHIV are on sustained ART, and 90%

of those on ART have a suppressed viral load (i.e. HIV-1 RNA <1,000 copies/mL), as shown in Figure 1.[6]

The total number of patients on ART in Malawi is currently about 800,000, representing close to 80% ART coverage in PLHIV. The survival benefit of ART on this scale has contributed to an increase in the life expectancy of the general population.[7] Such a large patient population requiring chronic care also places an enormous burden on the fragile health system. Simplified guidelines are needed to allow task shifting of the decision to start ART from physicians to non-physician clinicians and nurses.

In the Malawian public health approach, ART involves a limited number of standardized regimens. Initially, stavudine-lamivudine-nevirapine was the standardized first-line regimen. However, this caused frequent and severe side effects such as peripheral neuropathy, lactic acidosis, lipodystrophy due to stavudine, and severe hypersensitivity reactions due to nevirapine.[8, 9] Toxicities became much less common when this was replaced by tenofovir-lamivudine-efavirenz. Further improvement is expected with the planned introduction of a dolutegravir-based regimen in 2019. In case of failure on standardized first and second line ART regimens, Malawian PLHIV now have access to a third-line ART regimen, although very few patients are currently taking this.

CHALLENGES IN THE MALAWI HIV PROGRAMME

Despite the successes, a number of important challenges remain. First of all, sustainability of the programme cannot be taken for granted. The programme depends on donations, mostly from the United States (through PEPFAR) and the Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria. Second, the HIV programme is a vertical 'silo' in a country with a primary health care system that has much less financial support otherwise. Integration with other health services (family planning and hypertension clinics for instance) is limited. Third, patient attrition due to a combination of defaulting from treatment and death is considerable. In the national cohort that started ART eight years ago, only 50% of patients are still registered as 'alive and on treatment'.[6] Further challenges include HIV drug resistance, lack of tailored care for key populations (adolescents, sex workers and men having sex with men), and numerous patients still presenting with advanced HIV disease.

In the early years of the HIV programme, many patients who started ART had a low CD4 count and/or advanced clinical HIV disease (WHO clinical stage 3 or 4). The risk of death in the first year of ART was substantial. As the threshold for eligibility to ART was lowered over the years (by increasing the CD4 cell count level), fewer people initiated ART with an AIDS diagnosis and the 3-month mortality dropped steadily (Figure 2). Despite these positive trends, a remarkably large number of patients still present with advanced HIV disease, either due to late HIV diagnosis, defaulting from ART, or long-term ART failure. These patients are at high risk of dying, mainly from tuberculosis, cryptococcosis and severe bacterial diseases. This phenomenon is observed not just in Malawi but in the whole of sub-Saharan Africa.[10]

the benefit of enhanced anti-microbial prophylaxis (fluconazole, albendazole, ciprofloxacin and isoniazid), nutritional supplementation (with peanut butter based therapeutic food) and ART intensification (with raltegravir). The results showed that only anti-microbial prophylaxis reduces mortality, but it was not clear which of the antimicrobials contributed most to the result.[11] Two RCTs in Malawi, South Africa, Zambia, Zimbabwe and Uganda found that PLHIV admitted to a hospital benefit from screening for tuberculosis with urine lipoarabinomannan (LAM) testing in terms of reduced mortality, if it involves patients with clinical tuberculosis suspicion, severe anaemia and/or a low CD4 count.[12, 13] An RCT conducted in Tanzania and Zambia enrolled nearly 2,000 ART-naive adults with CD4 <200 cells/µL. The study showed that cryptococcal antigen screening in blood, followed by antifungal treatment if found positive, in combination with community-based support for ART adherence, improves survival.[14]

Following these study results, Malawi 2018 HIV guidelines have included lateral-flow cryptococcal antigen screening and urine LAM testing in

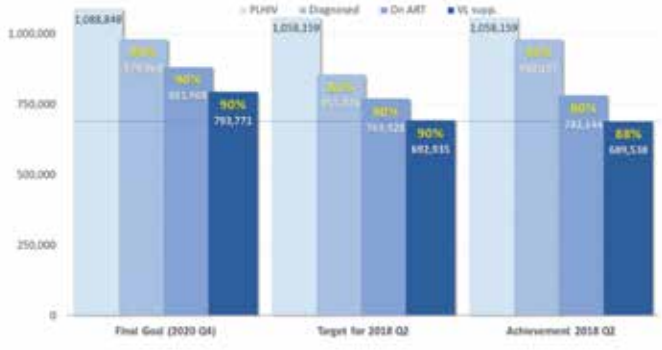

Figure 1: UNAIDS 90-90-90 targets and Malawi HIV programme achievement in June 2018 (copied from reference 6, with permission).

EVIDENCE-BASED INTERVENTIONS FOR ADVANCED HIV DISEASE

The REALITY randomized clinical trial (RCT) conducted in Malawi, Uganda and Zimbabwe enrolled patients with CD4 lower than 100 cells/µL. It tested all patients with advanced HIV disease, including all PLHIV admitted to medical wards of hospitals, whatever the reason for admission. In addition, implementation of isoniazid prophylaxis has started in high tuberculosis

THE MALAWI HIV PROGRAMME IS A MODEL FOR THE PUBLIC HEALTH APPROACH TO ANTIRETROVIRAL THERAPY (ART) IN SUB-SAHARAN AFRICA

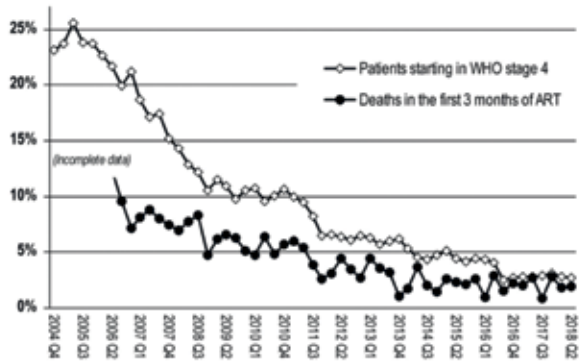

Figure 2: Patients initiating ART in WHO clinical stage 4 (i.e. with an AIDS diagnosis) and deaths in the first three months on ART as registered in June 2018 (copied from reference 6, with permission).

burden districts on top of cotrimoxazole prophylaxis, which has been part of the preventive package since 2004.

From a health systems perspective, the challenge of preventing advanced HIV disease is considerable with few evidence-based options. A promising new development is the 'welcome back clinics' to make it easier for those who have defaulted from ART to return to care. Likewise, efforts to better engage men in the health system are important, given that male gender is strongly associated with late HIV disease presentation.[15] Annual routine viral load monitoring, timely forwarding of viral load results to patients, and acting on these results by switching to next line ART, if indicated, can prevent long-term ART failure. However, this is expensive and poses logistical challenges.

CONCLUSION

Over the course of 15 years and under difficult circumstances, the Malawi Ministry of Health has built a high-quality, evidence-based HIV programme together with multiple stakeholder organizations. However, multiple challenges remain, for instance the continuing presentation of advanced HIV disease.

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PMTCT OPTIONS IN RESOURCE LIMITED SETTINGS IN 2011.[2]

WHO Option A (for women who are not eligible for triple drug ART due to their own health): Antepartum zidovudine started from 14 weeks' gestation; plus single-dose nevirapine at onset of labour, plus zidovudine/lamivudine during labour and delivery and continued for 7 days' postpartum

WHO Option B (for women who are not eligible for triple drug ART due to their own health): Triple drug ART started from 14 weeks' gestation until 1 week after exposure to breastmilk has ended Malawi's Option B+ (irrespective of whether women are eligible for triple drug ART due to their own health): Life-long, triple drug ART started from 14 weeks' gestation

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Paediatric HIV medicines: the right dose, the right taste

Despite significant efforts to increase the number of children on HIV treatment and reduce mother-to-child transmission of the disease, only 52% out of around two million children living with HIV worldwide received antiretroviral therapy in 2017, compared with 59% of adults. Without treatment, over half of children born with HIV will not live to see their second birthday.

One of the reasons that more children are not being put on antiretrovirals (ARVs) is the suboptimal variety of paediatric antiretrovirals available today. Pharmaceutical companies have invested little in developing child-appropriate drug formulations. One of the main treatment regimens currently recommended by the World Health Organization (WHO) for the youngest children was not designed with children's needs in mind – the medicines come in the form of syrups that are horrid-tasting and hard to administer, especially to children that have both HIV and TB, and moreover they require refrigeration.

There is also limited access to diagnostic tests for infants in resource-limited settings. Because of these unmet medical needs, children with HIV are a neglected population.

The Drugs for Neglected Diseases initiative (DNDi) is a not-for-profit research and development organisation that develops new drugs for neglected diseases such as paediatric HIV, human African trypanosomiasis, leishmaniasis, Chagas disease, filarial infections, mycetoma and hepatitis C. Together with partners, DNDi is working to deliver optimal child-adapted ARVs, with a special focus on infants and young children who are at the highest risk of dying if they do not have access to treatment.

THE FIRST STEPS TOWARDS OPTIMUM TREATMENT

In 2010, DNDi was asked by various organisations, including Médecins Sans Frontières/Doctors Without Borders (MSF), WHO, and the global health initiative Unitaid, to apply its expertise in neglected disease research and development (R&D) to the development of paediatric HIV treatments. DNDi established a paediatric HIV programme, and experts were consulted to build target product profiles of formulations for infants and children.

In 2012, Unitaid awarded USD 17.3 million to DNDi to support the development of a protease inhibitor (PI)-based first-line ARV regimen. WHO-guidelines published in 2013 recommended a regimen containing the PI lopinavir/ritonavir (LPV/r) as a first-line treatment for all children under three years old. Until recently, the only formulation available was a syrup that contains 40% alcohol.

IMPROVING OPTIONS FOR CHILDREN WITH HIV AND TB

DNDi is partnering with Cipla Ltd., an Indian company that produces generic medicines, to develop a solid first-line '4-in-1' fixed-dose combination of Abacavir/Lamivudine/Lopinavir/Ritonavir (ABC/3TC/LPV/r) for infants and young children under three years of age that meets WHO recommendations. DNDi's goal is to ensure that these easy-to-use formulations are affordable and can be rapidly introduced in countries with large numbers of eligible children.

To PrEPare countries for the 4-in-1 fixed-dose combination, DNDi and partners are introducing alternative optimised paediatric formulations and improving treatment options for children with HIV and TB. With its partners in South Africa, DNDi has addressed the negative drug-drug interactions between PI-based HIV treatments recommended by WHO and the TB drug rifampicin by providing essential evidence and data in support of a process known as 'super-boosting'. This negative 'drug-drug interaction' is a major barrier in treating children that have both TB and HIV – a problem that is especially acute in southern African countries at the heart of the HIV epidemic.

To address this issue, DNDi conducted a pharmacokinetic study in five hospitals in South Africa to demonstrate the safety and effectiveness of 'super-boosting', which involves adding extra ritonavir to the LPV/r regimen. Results recently published show that super-boosting is safe and effective for TB/HIV co-infected children.[1]

In 2015, Cipla licensed a solid '2-in-1' fixed-dose combination of lopinavir/ritonavir pellets (i.e. mini tablets to be mixed with food or liquids). This is a clear improvement over the lopinavir/ritonavir syrup, since it does not require refrigeration, and is an important step towards introducing the 4-in-1 once it is approved. To improve access to this interim 2-in-1 combination, DNDi has been running the LIVING implementation study in Kenya, Uganda, and Tanzania. Interim results of this study have been presented in various conferences, including CROI 2018 and the International AIDS Conference in Amsterdam in July 2018.[2,3] 82% of the children in the study were virologically suppressed at 48 weeks (viral

WITHOUT TREATMENT, OVER HALF OF CHILDREN BORN WITH HIV WILL NOT LIVE TO SEE THEIR SECOND BIRTHDAY.

load ≤ 1000 copies/ml), compared to a baseline of 59%. LPV/r pellets were well accepted with minimal safety concerns. Treatment naïve patients, those failing nevirapine as well as those switching from LPV/r liquid, were well suppressed at week 48 and had recuperated immunologically and clinically.

A comparable level of virological suppression at 48 weeks across weight bands was observed in children from 5-11 months, 12-24 months, 25-40 months and 49+ months. Finally, time previously spent on ART and the type of ART did not influence the virological suppression (IAS 2018). A qualitative sub-study (RE-LIVING study) assessing the acceptability of the LPV/r pellet formulation amongst caregivers, children and healthcare workers found that the formulation was highly acceptable to caregivers due to its ease of storage, discrete packaging, and lack of bitterness compared to syrups. It was also found to be highly acceptable to children if the mix of pellets and food or liquid could be given quickly before the development of a bitter taste.[4]

Importantly, the LIVING study has built clinical capacity in Kenya and Uganda – training health workers and caregivers in the administration of new, improved formulations. It has already recruited over 1000 children in routine clinical settings – a significant achievement in the field of paediatric HIV.

4-MEDICINES-IN-1 FORMULATION: INFANTS AGED 2 MONTHS - 3 YEARS

DNDi's long-term goal is to develop and deliver a taste-masked, heat-stable 4-in-1 LPV/r-based fixed-dose combination for infants and young children. This 4-in-1 fixed-dose combination (ABC/3TC/LPV/r 30/15/40/10 mg) will be simple to use with water, milk, breast milk, and food. In addition to improved taste-masking, the 4-in-1 has been formulated into granules, with individual particle sizes that are nine times smaller than the 2-in-1 pellets.

This reduction in particle size is a key step in developing the 4-in-1 formulation and will facilitate swallowing by young infants, some of whom experience difficulties swallowing the 2-in-1 pellets.

To provide clinical data in young HIV-infected infants and children, DNDi is PrEParing a study named LOLIPOP (lopinavir/ ritonavir/lamivudine/ abacavir as an easy-to-use paediatric formulation in a Phase I/II study). The LOLIPOP study will begin in Uganda in 2019 and will generate pharmacokinetic, safety, and acceptability data on the 4-in-1 to provide evidence for worldwide scale-up.

With regulatory approval foreseen for 2019, the 4-in-1 should provide a decisive improvement for paediatric HIV treatment: a PI-based, all-in-one ARV regimen that is safe and efficacious; suitable and palatable for infants and very young children; easy-to-use as it will be a fixed-dose combination; and that does not require refrigeration.

ENDING THE NEGLECT: MULTIPLE TREATMENT OPTIONS FOR CHILDREN

Another new and promising child-adapted HIV treatment based on dolutegravir (DTG), from the integrase inhibitors class of ARVs, is expected to be approved in the near future. Along with the 4-in-1, this means that two new treatments will be available for children, representing the most significant 'treatment revolution' for children with HIV since the advent of antiretroviral therapy, a situation that was almost unimaginable just a few years ago.

Efforts are now underway to establish the safety, efficacy, and appropriate dosing of DTG for children. While adults are being switched to DTG regimens as the result of a shift in WHO guidelines, it will take more time for younger children to benefit, as the dosage for children under six years of age and formulations adapted to very young infants have yet to be approved.

At the same time, regimens containing NNRTIs, such as efavirenz and nevirapine (with which the majority of HIV-positive children are currently being treated), will no longer be recommended because of poor viral suppression in children. The 4-in-1 will therefore play a critical role in closing the treatment gap for children with HIV.

Along with improvements in early infant diagnostic technology, these new formulations should contribute to ending the long-standing neglect of children living with HIV. Paediatric HIV still claims too many lives – now is the time to make improved formulations available for children.

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Towards an AIDS-free generation


PHOTO: SHUTTERSTOCK

HIV TREATMENT FOR CHILDREN IN SUB-SAHARAN AFRICA

Ending the AIDS epidemic among children, adolescents and young women by 2020: That is the ambition of the 'Start free, stay free, AIDS-free' program, launched by UNAIDS and PEPFAR in 2016. Much work still needs to be done to achieve this ambitious goal. Worldwide, an estimated 1.8 million children are living with HIV - the majority in sub-Saharan Africa.[1] Access to lifesaving antiretroviral treatment (ART) for these children has increased exponentially over the past twenty years, but with the increasing use of ART worldwide, the emergence of HIV drug resistance is an important threat to achieving an AIDS-free generation.

Various mechanisms make children living with HIV more vulnerable to developing HIV drug resistance. First, fewer antiretroviral drugs are approved for use in children, which makes it harder to switch to another drug in case of side effects or toxicity. Second, a growing child needs frequent dose adjustments to adapt the regimen to their changing pharmacokinetics and body weight, making accurate dosing difficult. Third, young children are dependent on their parents to receive their medication, who are often sick themselves or have even passed away. Older children might fear stigma when they disclose their HIV status to their peers, which limits their motivation to adhere to treatment. Finally, children who have been exposed to antiretroviral drugs perinatally, as a measure to prevent mother to child transmission (PMTCT) of HIV, have an increased risk of developing HIV drug resistance. In these children, HIV drug-resistant mutations may be present even before they start ART themselves, i.e. pretreatment drug resistance.

PRETREATMENT DRUG RESISTANCE

Relatively few data on pretreatment drug resistance in children are available. However, the studies conducted in sub-Saharan Africa (South-Africa, Swaziland, Cameroon, Tanzania, Central Africa Republic, Senegal, Uganda, Zimbabwe, Kenya, and Malawi) have shown an increasing prevalence over the past years. In a meta-analysis we found that 43% of children who were known to have been perinatally exposed to ART for PMTCT had pretreatment drug resistance. In children without PMTCT exposure, 13% had pretreatment drug resistance and this prevalence has increased significantly over the past years, from 0% in 2004 to 27% in 2013.[2] These figures imply that a growing number of children starting ART in sub-Saharan Africa have resistant viruses in their blood, against which the standard first-line treatment will not be effective. These children will not be able to achieve virological suppression with first-line therapy.

These worrying outcomes are reflected in the findings of a second meta-analysis we carried out. In this analysis, which included more than 51,000 children in sub-Saharan Africa and Asia, we found that after 12 months of first-line treatment only 65-73% of children had virological suppression, i.e. a viral load of less than 1000 virus copies/ml.[3] A comparable meta-analysis among adults in low- and middle-income countries found a much higher proportion of 85% achieving virological suppression.[4]

FIRST-LINE TREATMENT

In two cohort studies in Uganda and Nigeria, we enrolled around 500 HIV-infected children who were starting first-line ART and followed them for a period of two years. All children had a viral load test at treatment initiation and every six months thereafter. An HIV drug resistance test was done in children with a viral load of more than 1000 copies/ml. Both in Nigeria and Uganda we found that one in six children had pretreatment drug resistance. The majority of these children had not been perinatally exposed to ART. After two years of first-line treatment, 33% of the children experienced treatment failure of their first-line regimen, defined as either two consecutive viral load measurements >1000 copies/ml or death. The presence of pretreatment drug resistance was the most important predictor for treatment failure and increased the risk of failure by a factor of 7 to 15.[2,5]

At the start of this study in 2010, first-line treatment in both countries consisted of two nucleoside reverse transcriptase inhibitors (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI). Children under the age of three who were known to have been exposed to ART for PMTCT were prescribed a first-line regimen consisting of two NRTIs and one protease inhibitor (PI). However, it is often not known if a child has been exposed to PMTCT, especially in older children or if the mother has passed away. Since 2013, the World Health Organization therefore recommends that all children under the age of three be treated

with a regimen of two NRTIs and a PI. Unfortunately, PIs are more expensive than NNRTIs, and in many African hospitals these guidelines are therefore hard to implement in practice.

SECOND-LINE TREATMENT

Second-line treatment usually consists of two NRTIs and a PI. PIs have a higher genetic barrier and therefore resistance is expected to develop less frequently.[6] In Uganda, we followed a group of 64 children starting second-line therapy. After two years, 20% of these children experienced treatment failure. Drug-resistant mutations against PIs were found in none of these children.[7] This implies that treatment failure was most likely due to poor treatment adherence and not to HIV drug resistance against second-line drugs. This finding is reassuring, especially given the fact that third-line medication is virtually unavailable in sub-Saharan Africa. However, if treatment adherence remains poor, drug-resistant mutations will eventually develop. Measures to improve treatment adherence are therefore needed.[7]

In a multicentre analysis of children in Africa and Asia, we found comparable results, with 16% of children failing treatment after two years of second-line treatment. Remarkably however, adolescents (aged 10-18 years) had an almost four times higher risk of failure compared to younger children [8] Poor treatment results for adolescents living with HIV have been found in other studies as well, and adolescents are increasingly recognized as an important risk group for HIV-related morbidity and mortality. In sub-Saharan Africa, HIV is the leading cause of mortality among adolescents, whereas this is no longer the case for younger children or adults.[9] Worldwide, the number of AIDS-related deaths decreased by 24% between 2004 and 2011, but AIDS-related mortality in adolescents increased by 50% over the same time period.[10] These poor treatment results call for an increased focus on adolescents living with HIV, not only to improve morbidity and mortality in the individual patient, but also to prevent transmission of HIV in adolescents when they become sexually active.

CONCLUSIONS

Enormous strides have been made in the fight against HIV since the beginning of the millennium. Access to life-saving treatment has increased, and nowadays more than half of the world's population living with HIV is being treated with ART.[1] However, treatment outcomes for children on ART in sub-Saharan Africa still lag behind. The number of children achieving virological suppression on first-line ART is far below the so-called UNAIDS 90-90-90 target of 90% virological suppression to be achieved by 2020.[11]

The increasing prevalence of pretreatment drug resistance is a problem which will become increasingly important in the near future. Given the high rate of drug resistance against NNRTIs, it is important that WHO guidelines recommending PI-based first-line treatment are followed. For this to happen, drug prices need to go down, as the price of a PI is more than three times higher than of an NNRTI. Newer drugs such as integrase inhibitors could play an important role for children with HIV drug resistance, but these drugs are still almost not available in sub-Saharan Africa.

However, the development of potent antiretroviral drugs and improved access to these drugs in sub-Saharan Africa is not in itself enough to improve HIV care for children. Providing age-specific HIV care, including child-friendly formulations of drugs, and the implementation of adherence support programs are also needed. A combination of all these measures is needed to assure a healthy and productive future for children and adolescents living with HIV in sub-Saharan Africa and for achieving an AIDS-free generation.

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Early detection of side effects after ART initiation: a challenge in Malawi

THE SETTING

This case report originates from St Luke's Hospital, a rural mission hospital in Malosa, southern Malawi. The hospital possesses 175 beds with access to laboratory testing, ultrasound and X-ray imaging for diagnostics. The hospital provides a comprehensive HIV care program and serves as a referral hospital for several health centres in the region. These health centres provide basic primary healthcare with laboratory services limited to microscopy and rapid diagnostic tests. Additionally, they provide anti-retroviral therapy (ART) free of charge. The nearest third-line (governmental) hospital with an Intensive Care Unit is located 30 minutes from our hospital by private transport.

CASE

A 40-year-old HIV-positive woman was referred to our hospital because of a reduced level of consciousness. Three days prior to referral, the patient went to her health centre because of jaundice, general body weakness and nausea lasting one week. There was no fever, abdominal pain, vomiting or decolorized stools. She was a non-smoker, and there was no history of herb or alcohol abuse.

Four months earlier, the patient tested positive for HIV and was immediately started on ART according to the local protocol: Tenofovir, Lamivudine and Efavirenz. As she had recently started HIV treatment, the medical assistant thought that the complaints could be side effects of ART, and the patient was advised to suspend the therapy.

On the day of referral, the woman was brought in to the health centre because her symptoms were progressive and she had lost consciousness. On admission in our hospital, the patient's Glasgow Coma Scale was 6/15. The vital signs are summarized in Table 1. Despite severe jaundice, no other abnormalities were observed on physical examination. There was no wasting, neck stiffness, lymphadenopathy or oral thrush. The laboratory results are shown in Table 2. Abdominal ultrasound showed a shrunken, homogenous liver with some ascites. The gallbladder, bile ducts and spleen appeared normal.

Table 1: VITAL SIGNS ON ADMISSION

Temperature	37.5 C
Blood pressure	95/55 mmHg
Pulse rate	115 beats per minute
Saturation	99% on room air

The initial management consisted of broad spectrum antibiotics and intravenous fluids. After the laboratory results (Table 2) became available, suspicion of hepatic encephalopathy was raised. In the absence of other risk factors, i.e. negative Hepatitis B and C tests and non-dilatated bile ducts, toxic liver injury due to Efavirenz was strongly suspected and Prednisolone 1mg/kg/day was started. Unfortunately, the patient deteriorated rapidly and she passed away only 36 hours after admission. Although the diagnosis of a severe adverse reaction to Efavirenz cannot be made with absolute certainty, it is the most likely cause of the severe hepatic injury in this case. Sadly, despite early recognition and adequate initial management by the health centre, the patient did not survive.

BACKGROUND OF ART INDUCED LIVER INJURY

Antiretroviral drugs are increasingly available in less developed/low-resource countries and have a tremendous impact on life expectancy in HIV-infected people. However, ART may induce side effects, and hepatotoxicity is one of the most serious ones. Non-nucleoside reverse transcriptase inhibitors like Efavirenz are the most common cause of hepatotoxicity among ART subgroups. Most at risk are those treated with Nevirapine, those with pre-existent liver disease, and those who are treated with protease inhibitors as well.[1] In previously described case series, the onset of Efavirenz induced hepatotoxicity occurred between two and twenty-four weeks after initiation of treatment.[1-3] Although hepatotoxicity is usually mild and reversible after withdrawal of the Efavirenz, cases of Efavirenz induced fulminant liver failure have been described.[2,4,5] If patients with severe liver injury do not improve after interruption of Efavirenz, treatment

Table 2: LABORATORY RESULTS

		Normal values
Haemoglobin	9.1 g/dL	(13.0-17.0 g/dL)
White blood cells	13.7x10^9/L	(4.0-10.0x10^9)
Platelets	389 x10^9/L	(100-300x10^9)
ALT	141 U/L	(<34 U/L)
AST	91 U/L	(<31 U/L)
GGT	120 U/L	(6-45 U/L)
ALP	1060 U/L	(64-306 U/L)
Conjugated bilirubin	11.9 mg/dl	(<0.3 mg/dl)
Total bilirubin	27.9 mg/dL	(<1.2 mg/dl)
Albumin	2.7 g/L	(3.3-5.5 g/l)
Creatinine	1.0 mg/dL	(0.5-1.1 mg/dl)
Urea	17.0 mg/dL	(10-50 mg/dl)
Random blood sugar	194 mg/dL	(60-133 mg/dl)
Hepatitis B/C	Negative	
Cryptococcal antigen test (serum)	Negative	
Malaria rapid diagnostic test	Negative	

with corticosteroids should be considered, although the evidence is limited and should be further investigated.[6,7]

In Malawi, Tenofovir/Lamivudine/Efavirenz is a first-line ART regimen and frequently the first choice when starting on ART. While starting ART is daily routine matter in every Malawian hospital, there are actually also major challenges involved as presented in our case. Although regular follow-up during the first months of therapy is recommended in the national protocol, laboratory resources are scarce and patient education regarding potential side effects is often limited. We presume that patients with ART induced liver injury are often missed and underreported. Increased awareness on the potential lethal side effects of ART and improved access to laboratory services can avoid unnecessary delay in changing the ART regimen, and this can save a patient's life.

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I am HIV positive and I am fine!

I became infected with the HIV virus in 1986. It was in the middle of the horrible panic period about this new gay-related disease – a period in which nobody really knew anything about its modes of transmission. People were afraid to hug me or shake my hand. Coughing in a room with other people felt like a murder attack to them.

Thirty-two years later, much has changed in terms of treatment and care, but many things have not changed. Ignorance and stigma still exist in many low- and middle-income countries, as well as here in the North. This motivated me to make a film about the stigma surrounding HIV and AIDS. In this film, Speak Out, members of a support group courageously tell their story. Terribly sad stories, in particular those of the more vulnerable persons like single mothers, young gays and orphan teens. Their testimonies, unfortunately, illustrate how little progress we have made in this regard. Group members would not talk about their situation to their family members, afraid of consequences such as having to leave their homes or in some cases even worse. I kept asking myself why. We have the evidence, the options of treatment, and means to prevent mother to child transmission. And we educate people. So what did we miss?

Visiting South Africa and meeting members of this support group made me feel ashamed about my privileged situation – white, male, and rich – and I was shocked by the impact of the stigma. Thirty years ago, people's fear was based on lack of knowledge. Apparently things haven't changed that much. After showing the film at a theatre school in the Netherlands, some of the students asked me how the virus is transmitted. The ignorance on both sides of the equator is alarming. For us, getting infected may not be a big deal anymore, as the infection is treatable. But this lack of focus is cynical and selfish, and it contrasts sharply with the reality in many countries, where the disease is difficult to control and even on the rise due to a persistent lack of education and moral judgment regarding those living with HIV.

I became a so-called 'long-term survivor'. In the beginning, I didn't speak out because of the stigma. Only after people knew more about the disease, did I feel comfortable enough to disclose my situation. But I also wanted to live a normal life. In the end, I was more than just my disease. So I often chose not to speak out. But now I feel the need to raise my voice on behalf of those who are afraid to speak, or even risk their lives when doing so. I continue the fight against ignorance and discrimination, now even more so in a world with rising conservatism. Because of Trump's enactment of the Mexico City Policy, sexual education programmes are being curtailed or banned, as was recently the case in South Africa. Since the disease is no longer life-threatening here in the West, I fear that we are also losing our sense of solidarity. This calls for action!

I admire the courage of people like Lizzy, a member of the support group – a 52 year old Zambian woman who works in Johannesburg to support her family in Lusaka. She looks into the camera and is not afraid to say: 'I am HIV positive and I am fine! The medication is taking care of me, and I am taking care of myself and my family. A couch is a couch, and I'm not transmitting the disease. I am fine!'

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Speak Out!

2018 | English | 38 mins | Digital Video | Color | Stereo | 25fps

In 1986, at the peak of the panic about a new 'gay-disease', director Jan van Opstal heard that he was HIV-positive. Years of stigma followed, but the panic waned and life continued. During a holiday in South Africa, Jan was introduced to the Sister Mura Foundation, a support group for people with HIV. Many of the group members where shunned from their home countries, sometimes by their family fearing infection. The taboos surrounding HIV and AIDS echoed Jan's own experience, but the contrast to his own situation struck him. He started following the members of the support group and sharing experiences together. The result is a touching documentary that calls for solidarity and discusses the importance of speaking out.

The film is available for educational purposes. Contact: janvanopstal@hotmail.com

FACTFULNESS

Author: Hans Rosling
Published by: Flatiron Books, 2018
259 pages, € 22.50

In Dutch: Feitenkennis,
published by Unieboek | Het Spectrum

We all know Hans Rosling, the world's most famous public health professor from the Swedish Karolinska Institute and co-founder of the Gapminder Foundation (see www.gapminder.org). A year after he died in February 2017 at the age of 68, his last work was published, the book FACTFULNESS, which he wrote together with his son Ola and daughter-in-law Anna.

WHY A BOOK?

After his very successful TED talks and lectures all around the world, Hans wondered why people are still so ignorant about basic facts of the world. During his worldwide war on ignorance, he was armed with statistics and could explain them in the most appealing ways, for example with the famous bubble charts (Figure 1). However, the more people Hans tested, the more ignorance he found, and this was true in all possible audiences ranging from students to NGO-workers and policy makers. This frustrating and worrying finding was why he wrote this book about why we tend to have a dramatic instead of fact-based worldview. When Hans was diagnosed with cancer, he cancelled all his talks and travels and devoted all his energy to finishing this book.

WHY WE ARE BIASED AND HOW TO AVOID IT

In his typical clear and amusing but serious way, Rosling describes ten unhelpful instincts we all suffer from, which lead to a biased world view. The first is 'the gap instinct' - the idea that there is a huge gap between us (the developed, rich world) and them (the developing, poor world). But 'there is no gap. Today, most people, about 75 percent, live in middle-income countries, not poor and not rich but somewhere in the middle, and starting to live a reasonable life'. Instead of just condemning all of us who often follow our gap instinct, Rosling gives us a way to tackle it by dividing the world into four income levels. People in level 1 live in extreme poverty (less than 1$ a day); most people live on level 2 or 3, and people on level 4 are rich (more than 64$ a day). This concept of 4 income levels seems a very useful and more accurate way to understand today's world, and it runs as a common theme throughout the book.

In each chapter, Rosling describes a different instinct that we tend to use when we think about the world, for example the straight-line instinct (the world population is just increasing), the destiny instinct (things have always been this way and will not change) or the blame instinct (there is a clear, simple reason for why something bad has happened). And in each chapter, he brings the good news on how these biases can be attacked by simple rules of thumb. This makes the book so appealing. It helps you realize your own misconceptions about the world, the reasons why they exist and where they come from, and at the same time gives you tools to fight them.

READ OR NOT?

Bill Gates said this was 'one of the most important books I've ever read'. And I fully agree. If you have not done so yet, let this be the next book you read. It is an absolute must-have, an ode to statistics and public health, and a valuable legacy from one of the world's greatest public health experts.

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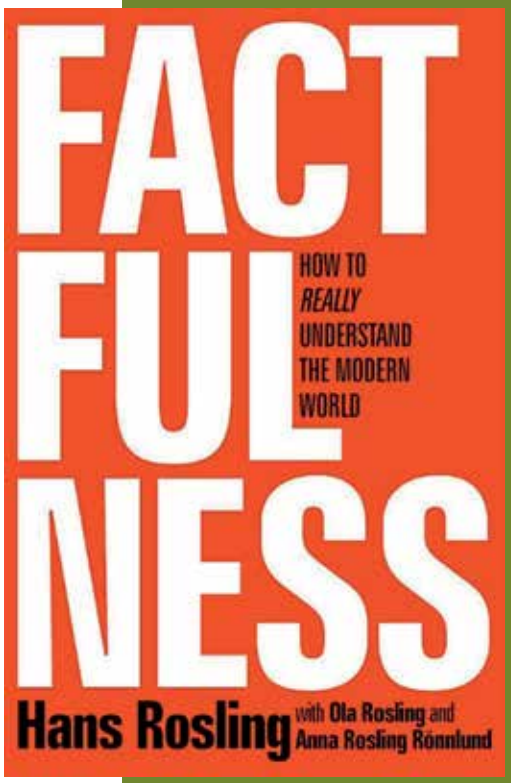

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