**HIV Treatment in sub-Saharan Africa:
Did bureaucratic headwinds delay access to dolutegravir?**

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Introduction

The World Health Organization now recommends dolutegravir (DTG) as part of the preferred first-line treatment for all adults living with HIV including women who may become pregnant. The new regimen with its high barrier to resistance, shortened time to suppression, superior side effects profile, and lower health sector and individual costs, represents a significant improvement. The recommendation removes an important obstacle to accessing dolutegravir as an essential element in controlling the epidemic.

Discussion

Translating science to policy to HIV service delivery is complex and vulnerable to significant delays. WHO, assuming a regulatory role, used preliminary Botswana *Tsepamo* study information regarding neural tube defects to issue a “safety signal” regarding DTG in May 2018. Regulatory evaluations of rare adverse reactions are complex, take time, and require considerable subject area specific expertise. After over a year, the WHO reversed its initial findings and issued revised treatment recommendations. However, the mixed messaging and confusion around dolutegravir’s safety profile has delayed national level adoption. The pace of national adoption of new WHO recommendations is measurable through published national guidelines and/or circulars available in the public domain. After 2015, published guidelines for 22 of 46 sub-Saharan countries (94% of 2018 regional HIV burden) showed that only three countries representing 4% of regional burden have adopted the new WHO preferred 1st line recommendations.

Conclusions

Monitoring and evaluating the translation of science to service delivery is a critical element of successful disease control and elimination. The DTG false alarm and ongoing delayed access provides an opportunity to learn valuable lessons and implement corrective actions. However, lessons can only be learned by accurately describing and examining the timeline, processes, and impact of policy decisions that can adversely impact millions of people living with HIV. As with any successful global disease elimination effort or major project, it is important to establish a critical pathway for translation of science to service delivery and hold people and agencies accountable for their roles in accelerating and/or delaying progress.

Introduction

After years of confusion and uncertainty, the World Health Organization has recommended dolutegravir as preferred first line treatment for all adults living with HIV including women who may become pregnant. These recommendations end a serious roadblock to deploying this important HIV medicine and controlling the epidemic. As part of the new preferred Tenofovir, Lamivudine, and Dolutegravir (TLD) HIV treatment regimen, it's high barrier to resistance, shortened time to suppression, superior side effects profile, and lower costs, represent a significant improvement over the previous recommendations.

Dolutegravir, an integrase inhibitor, was approved by the United States Food and Drug Administration in 2013 (1). At least three randomized clinical trials--SPRING (2013), SINGLE (2015) and FLAMINGO (2015)-showed evidence of non-inferiority and in some cases superiority while others supported the use of DTG in treatment-experienced patients (VIKING and SAILING) (2) (3) (4) (5) (6). Dolutegravir has many features of an anchor of a first-line regimen including efficacy and tolerability in men, women, and children at least 30 kilograms, daily low dosing, and ease of co-formulation with other antiretrovirals (7). Additionally, its safety profile and relative lack of adverse effects allows for fewer laboratory tests, higher adherence, 6 month prescriptions, and cost-savings for individuals and the health sector. Recent studies comparing a two-drug regimen that includes dolutegravir with a classic three drug regimen show non-inferiority in treatment naïve individuals, adding another simple, well tolerated inexpensive option to existing HIV treatment options (8) (9).

Dolutegravir and integrase inhibitors have emerged from a robust HIV drug development pipeline as a direct result of years of community activism, scientific research, and the investment of hundreds of millions of taxpayer and private sector dollars (10). While bringing this new class of anti-retroviral from bench to the pharmacy has been a success in most wealthier countries, access for the majority of people living with HIV in lower- and middle-income countries has been delayed. Given its obvious potential, understanding the reasons behind the delay may help provide lessons for future translation of science to service delivery efforts.

Translation of science to global policy

The translation of science to policy to HIV service delivery is complex and vulnerable to significant delays. Although eventual translation to impact individual and public health is often the stated objective for most research projects, it is usually unmonitored and rarely

evaluated. There are multiple examples in HIV control suggesting it can take over 10 years for a scientific discovery to reach the people who could benefit (11) (12) (13) (14) (15). Small but sometimes significant delays occur along the many stages from discovery through regulation to global policy formulation to national recommendation to funding to service delivery and access at the individual and community level. While some aspects of the pathway have been examined in detail (16) (17, 18), focusing on the overall process is usually left to community activists and non-governmental organizations concerned with access (17) (19) (20). However, aside from moral suasion and direct action, these organizations often lack the means to ensure accountability. The number of activists and organizations is limited and many have resources and funding for only specific aspects of the response. Monitoring and evaluating access to treatment and improved treatment regimens competes with other policy priorities such as prevention (usually without including treatment as prevention), access to PrEP, vaccines, fighting discriminatory laws, and/or increasing research funding (21) (22) (23). Perhaps most importantly the translation of science to service delivery process is often complex and opaque making it difficult to establish accountability among the leadership and junior staff controlling the many parts of the political and technical process. Leadership decisions leading to significant delays may only be noticed by a few privileged experts, staff, and activists inside the process and usually go unchallenged. Conflicts of interest, whether financial, scientific, may also include the desire to “not rock the boat” to remain involved in expert committees or as staff. Despite increased attention to elaborating conflicts, many conflicts fall outside routine consideration. Although serious, they are often unspoken and may dampen criticism or the willingness to discuss controversies or delays in the public domain.

For HIV, the process from discovery through regulatory approval has been the focus of considerable community activism and efforts to bring about transparency, accountability and efficiency (23) (17) (19) (20, 22). However, after regulatory approval, formulating global policy and the subsequent adoption into national policy is a similarly complex political process that is opaque to most of the stakeholders. The lack of monitoring and evaluation of this process and accountability favors conservative decision-making and delays (24-27). Constituencies are often vulnerable people living in multiple countries on less than a dollar a day—people without voice who are often only nominally represented on the many expert committees and as members of agencies by only a few poorly-financed international activists. Consequently, there is a high risk for framing policy questions from a narrow abstract

institutional perspective with downside considerations involving institutional risk often outweighing the upside potential for individuals and the community. Leadership is rarely held accountable for disease control strategy failures based on poor policy decisions and/or delays in issuing new strategies or policies. Delays and poor policy decisions have, in some cases, squandered scarce resources and cost millions of lives.

Global policy monitoring and evaluation

An accurate assessment of policy success and failures is critical to ensure that robust processes are in place for current and future disease control efforts. However, history is usually written by the victors and delays or poor decisions often remain unidentified and/or unexamined. Agency-sponsored commentaries such as “*Global HIV treatment: headwinds turning to tailwinds*” (28) often fail to capture many of the major flaws that continue to plague international HIV policy development. Contrary to the commentary and press, the historical record provides a different perspective on the events leading to WHO approval of DTG as part of the first-line regimen (Figure 1).

The “*headwinds*” slowing access to DTG that are mentioned in the commentary are not recent and were there well before the dolutegravir “safety signal” (28). Although it was approved for first line therapy and the United States (2013) and Europe (2014), the World Health Organization (WHO) 2016 treatment guidelines did not recommend dolutegravir (DTG) as the preferred first-line regimen (29). The WHO’s 2016 treatment recommendations (29), May 2018 “safety signal” (30), 2018 treatment guidelines (31), and more recent delays in communicating new safety evidence (32) greatly slowed or blocked the transition to DTG as first line by most countries in Africa. The recommendations were ambiguous—they advised that women of childbearing age could receive dolutegravir if they had access to consistent and reliable contraception. The recommendations added to the confusion by highlighting the uncertain evidence regarding the safety of dolutegravir before and during pregnancy—something common with many or most drugs that are brought to market. The uncertainty and relegation to an alternate regimen also likely contributed to delays in both lowering the cost of DTG and the overall costs of delivering HIV treatment. DTG as part of TLD has the potential to greatly simplify treatment initiation while lessening the burden on heavily impacted clinical services. Reducing the clinic and laboratory burden on both clinicians and patients is a key aspect of achieving epidemic control and reaching at least 95-95-95 to prevent illness, death and transmission.

WHO dolutegravir danger warning

Preliminary data from the Data Safety Monitoring Board from the Botswana *Tsepamo* clinical study reported 4 neural tube defects (NTD) among 426 women on DTG with an estimated 0.94% (95% CI 0.26%–1.45%) risk (30) (33). This was higher than the estimated background rate, however, background surveillance for peri-natal outcomes, including the incidence of NTDs, in Botswana and the rest of sub-Saharan Africa has been plagued by lack of resources, attention and methodological challenges (34) (34) (35) (36). Assuming a regulatory role, WHO used the preliminary study data to issue a “safety signal” or warning in May 2018.

Regulatory evaluations regarding the safety of new medicines are complex, take time, and require considerable subject area specific expertise to evaluate potentially confusing or incomplete data. Clinical studies, whereby the event is then followed by an investigation, are methodologically inadequate to identify exposures for rare adverse drug events, particularly for those involving pregnancy. They are even more problematic as they are often based in hospitals and clinics, assuring that some peri-pregnancy related events will go un-noticed or reported. While a greater number of different types of neural tube defects were reported in the dolutegravir exposure arm, the study design precluded interviewing the women to determine potential exposures and causality—this represents a missed opportunity to interview the women regarding risk factors for NTDs including history of previous NTDs, medications, use of traditional medicines, substance use, other potential toxins, and whether they had received folate. This information was also not available pre-event thus further highlighting the weakness of using relatively small observational cohorts to look retrospectively for associations between exposures and extremely rare adverse outcomes. Even if the increased risk was accurate, the WHO “safety signal” warning did not include an analysis and/or discussion of the significant individual and public health downsides of using the preferred regimen with efavirenz. These include increased side effects and a significantly slower time to viral suppression with consequent increased risk of preventable illness and/or HIV transmissions for millions of people. Most importantly, the input of women who would be faced with weighing evidence and the risks and benefits of the regimen was not considered as part of deliberations around the safety signal. The lack of balance in weighing the benefits and risks for women, partners, and their children prompted the July 2018 Kigali Meeting and Communique calling for women to have a greater voice in decisions regarding their choices around HIV care and treatment (37).

About the same time as the “safety signal”, the Botswana *Tsepamo* study data were updated in May 2018 to include 596 births. Among these women receiving DTG at conception there were no additional NTD--the revised risk proportion was lowered to 4 of 596 or 0.67% (95% CI 0.49-1.05%) (33). In July, Brazil reported that their national birth surveillance system did not find an elevated risk for NTDs (38). Other national birth defect surveillance systems, including in the United States, suggested that DTG could be safely used. Despite the mounting evidence that called into question the initial interpretation of the data, the lack of solid background information on the national incidence of NTDs, the weighing of the relative risks of TLE vs DTG based regimens, and the caveats necessary when interpreting a post-hoc clinical trial, the safety signal was not rescinded and instead the decision was taken to wait for more data. Meanwhile WHO’s safety signal and the 2018 ART guidelines with its complicated warning regarding use of DTG in pregnancy had its effect (7). Most countries slowed adoption, some issued warning notices regarding the dangers of using DTG during preconception, and many stuck with the inferior TLE regimen for both men and women.

The national adoption of new WHO recommendations is measurable through an analysis of published national guidelines and/or circulars available in the public domain (24). While newspaper reports, surveys of agency staff, and other methods are useful to get a sense for the shifts in practice most clinicians and public health providers in the public sector follow official government policies. We reviewed the post-2015 published guidelines for 22 of 46 countries (94% of the regional HIV burden in 2018) (Table 1). DTG is not recommended in 14 of these countries representing 61% regional HIV burden (Figure 2). Only eight countries (33% regional HIV burden) include some recommendations on DTG in their guidelines but they vary considerably. As is recently recommended by the WHO, DTG is included in the preferred 1st line regimen for all adults and adolescents in only three countries (Botswana, Eswatini, Lesotho; 4% regional burden). In four countries with large HIV epidemics and a quarter of the regional HIV burden (Kenya, Zambia, Nigeria, Uganda), DTG is not recommended in the preferred or alternative 1st line regimen for pregnant women due to earlier data on lack of efficacy/safety of DTG in this population group. People living with HIV and TB are also excluded in Nigeria and Uganda. National adoption of global policy in other disease control efforts such as polio eradication or Ebola control is often fairly rapid and uniform. However, HIV policy adoption is complex and can lag for many years after a shift in the global recommendations (24). The reasons for delayed or partial adoption of the new science and policy around dolutegravir are multiple and decision making at the national

level, as is the case at the global level, is also vulnerable to delays due to influence from staff belonging to international agencies, major donors, non-governmental organizations, and universities.

Impact of delayed response to new data

Publishing in a top tier journal is time-consuming and is susceptible to significant delays. The peer-reviewed article on the *Tsepamo* results was eventually published over 15 months from the safety signal (39). Coinciding with the publication and meeting embargo, the findings were presented at International AIDS Society meeting in Mexico (40) where the WHO also issued its revised 2019 treatment recommendations (41). The WHO update was intended to settle the uncertainty around their previous interim recommendations. The new strong recommendations are unambiguous and recommend dolutegravir-based antiretroviral therapy (ART) as the preferred first-line regimen for all adults and adolescents with HIV(41). While welcome, the peer-reviewed publication of the article and release of the guidelines at a major international meeting begs the question whether it would have been possible to draw conclusions from the preliminary data last fall or earlier in 2019. The timing suggests that the delay may have been partially the result of the conflict of interest of waiting for publication in a prestigious journal and/or embargoes to ensure the timing of the announcement to coincide with a large international meeting.

The impact of the delay in releasing the data and the revised recommendations is difficult to calculate. There are 23 million people on HIV treatment, many on inferior regimens, and the negative consequences can likely be measured in millions of avoidable deaths and transmissions due to delays in achieving suppression, lack of adherence, and the development of resistance. Additionally, approximately 15 million other people living with HIV are not on successful treatment—did the lack of a more effective, easier to administer, and tolerable TLD option impede access for harder to reach people living with HIV? Speed matters and the DTG case suggests that there is considerable room for improvement in translation of scientific evidence to service delivery.

The DTG “safety signal” episode is not new and reminiscent of the previous warnings and delays in accepting efavirenz for use in women (42) (43). More than a decade ago, controversy around the adoption of efavirenz based on a study in non-human primate (44), highlighted the difficulties of decision-making around rare events and demonstrated the importance of surveillance and pharmacovigilance. However, a decade later surveillance

around the prevalence of birth outcomes for women remains weak in most countries. Similarly, there was a significant delay before translating the science around the importance of earlier ART initiation, with some arguing that WHO delayed recommending “test and treat” to prevent illness, death and transmission by a decade or more (13) (12) (24). Progress in improving access to effective pediatric formulations has also often lagged behind adult formulations (18). Similar to delays in drug access, access to new game-changing diagnostics including HIV self-tests have only reached a few hundred thousand people in Africa, mainly through pilot studies. In the case of HIV self-testing, the delayed access for millions of people who could benefit from the new technology dates from the mid 1990’s (45) (46) (47) (48). Additional delays are common in the national adoption of global diagnostic and treatment recommendations, as local expert committees, influenced by researchers and others, often take a conservative route including waiting for years for the results of multiple local pilot research studies (49) (50) (24).

Conclusion

The DTG false alarm and policy failure provides an opportunity to learn valuable lessons and solidify commitments to implement corrective actions. However, these lessons can only be learned by accurately describing and examining the timeline, processes, and impact of policy decisions that can adversely impact millions of people living with HIV. Adoption of new recommendations at the national level also bears scrutiny especially given the important role of locally based international donors, researchers, and implementers in supporting and/or blocking proposed national policy changes. Additionally, it is critical to describe conflicts of interest and other factors that may compromise rational decision-making around new policies and/or strategies. As in surveillance for disease incidence and prevalence, monitoring and evaluation of translation of science to access is a critical element of successful disease control and elimination. Specifically, as with any major project, it is important to set forth a critical pathway and hold people and agencies accountable for their roles in accelerating and/or delaying progress towards objectives such as 95-95-95. If a society can do it for major complex projects including building jet fighters and missile systems, why not for HIV elimination and other major disease elimination efforts? HIV remains a global public health threat of unprecedented proportions and there is a need to pull together while looking forward, however, evaluating past performance may help us accelerate our efforts to reach 95-95-95 and end the epidemic.

Table 1: Recommendations on the use of dolutegravir in the 1st line regimens for sub-Saharan African countries (2015-2019)

	Country	ART Guide lines	ART eligibility criteria	People living with HIV	PLHIV receiving ART	ART coverage	AIDS-related deaths	Recommendation on Dolutegravir (DTG) in the 1 st line regimens
1	Angola	2015	<500	330,000	88,734	27%	14,000	Not recommended
2	Botswana	2016	Treat all	370,000	307,377	83%	4,800	Truvada + Dolutegravir (for adults, adolescents and pregnant women)
3	Burundi	2016	Treat all	82,000	65,483	80%	1,900	Not recommended
4	Cameroon	2015	<500	540,000	281,083	52%	18,000	Not recommended
5	Cote d'Ivoire	2015	<500	460,000	252,127	55%	16,000	Not recommended
6	Democratic Republic of Congo	2016	Treat all	450,000	256,486	57%	13,000	Not recommended
7	Eswatini	2018	<500	210,000	177,156	84%	2,400	TDF+3TC+DTG (TLD) is the preferred first line regimen for all
8	Ethiopia	2017	Treat all	690,000	449,962	65%	11,000	Not recommended
9	Ghana	2016	Treat all	330,000	113,171	34%	14,000	Not recommended
10	Kenya	2018	Treat all	1,600,000	1,067,636	67%	25,000	For ≥15 years (or ≥ 35 kg body weight): TDF + 3TC + DTG (TDF + 3TC + EFV for women & adolescent girls of childbearing potential)
11	Lesotho	2016	Treat all	340,000	206,298	61%	6,100	TDF + 3TC + DTG (for adults, adolescents and pregnant women)
12	Liberia	2017	Treat all	39,000	13,880	36%	1,800	Not recommended
13	Malawi	2016	Treat all	1,000,000	814,275	81%	13,000	Not recommended
14	Mozambique	2016	Treat all	2,200,000	1,212,562	55%	54,000	Not recommended
15	Namibia	2017	Treat all	200,000	184,245	92%	2,700	Not recommended
16	Nigeria	2016	Treat all	1,900,000	1,016,346	53%	53,000	Alternate 1 st line regimens TDF + 3TC (or FTC) + DTG (adults & adolescents excluding pregnant women & TB/HIV co-infected) ABC + 3TC (or FTC) + DTG (for adolescents only)
17	Rwanda	2016	Treat all	220,000	193,726	88%	2,900	Not recommended
18	South Africa	2016	Treat all	7,700,000	4,788,139	62%	71,000	Not recommended
19	Tanzania	2017	Treat all	1,600,000	1,108,728	69%	24,000	Alternate 1 st line regimens TDF+(3TC or FTC) +DTG ABC+3TC+EFV600 or DTG AZT+3TC+EFV600 or DTG TDF+(FTC or 3TC) +DTG is the preferred regimen for PWID
20	Uganda	2016	Treat all	1,400,000	1,004,004	72%	23,000	Alternate 1 st line regimens ABC+3TC+DTG TDF+3TC+DTG (efficacy/safety in pregnancy and TB/HIV unknown)
21	Zambia	2018	Treat all	1,200,000	964,689	80%	17,000	Preferred first line: TDF or TAF + XTC + DTG • If HIV/TB and on Rifampicin, DTG 50mg twice daily • If pregnant or DTG not available: TDF + XTC + EFV (400mg)
22	Zimbabwe	2016	Treat all	1,300,000	1,150,543	89%	22,000	Not recommended

*Table shows recommendations from 22/46 sub-Saharan African countries (64% global HIV burden and 94% regional burden in 2018) that published guidelines between 2015-2018. Guidelines were published before 2015 or not available for the remaining 24 countries (6% regional HIV burden). All data are from 2018 (source: UNAIDS aids info).

Figure 1: Timeline of Dolutegravir Approvals, Safety Signal and Revision of Safety Signal Recommendation, 2013-2019

Figure 2: Recommendations on the use of dolutegravir in the 1st line regimens for sub-Saharan African countries (2015-2019)

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