Technical consultation on antiretroviral treatment optimization and strategies for access to dolutegravir in Latin America and the Caribbean from a public health perspective

Brasilia, 6-7 June, 2017

Meeting report

This short document summarizes the conclusions from the *Technical consultation on antiretroviral treatment optimization and strategies for access to dolutegravir in Latin America and the Caribbean from a public health perspective* held in Brasilia in June of 2017 and includes some additional updates related to optimization of antiretroviral treatment (ART) and access to new antiretroviral drugs in the Region.

The meeting was co-organized by the Government of Brazil, through the STIs/AIDS and Viral Hepatitis Department of the Ministry of Health, the Medicines Patent Pool (MPP) and the Pan-American Health organization (PAHO)/World Health Organization (WHO). The main objective of the meeting was to discuss with Latin American and Caribbean (LAC) countries and key partners opportunities and technical cooperation needs for treatment optimization and transition to dolutegravir (DTG) based 1st line ART, prioritizing countries with evidence of higher levels of pre-treatment resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs), and based on WHO recommendations for ART and HIV drug resistance (HIVDR) management and other feasibility and cost-effectiveness analysis.

Participants: government representatives from 17 LAC countries (Argentina, Bahamas, Barbados, Brazil, Chile, Costa Rica, Cuba, Ecuador, Guatemala, Haiti, Mexico, Nicaragua, Panama, Paraguay, Peru, Uruguay), civil society representatives from 5 LAC countries (ABIA from Brazil, REDBOL from Bolivia, AIS from Guatemala, AIS LATCA from Peru, and JASL from Jamaica), PAHO/WHO and key global and regional partners, such as (MPP, PEPFAR/USAID/CDC, Global Fund and Huésped Foundation. **The meeting concept note and agenda are included as Annexes 1 and 2. All the presentations from the technical consultations may be downloaded from the following link:** https://www.dropbox.com/sh/iqj4v2kn1y9psqo/AAAlnJD7dX9ZWNwslOnYpA6za?dl=0

The first day of the consultation participants reviewed current progress and challenges in the expansion and optimization of antiretroviral treatment in LAC. Among the most relevant advances: the early uptake of the WHO “treat all” recommendation with increase in the number of people on treatment and ART coverage; the adoption of the Treatment 2.0 initiative aligned with WHO guidelines (ART optimization, standardization and transition to preferred regimens, use of fixed dose combinations (FDC), reduction in the number of regimens, phase-out of non-recommended ARVs, use of WHO

prequalified low cost generics, etc.); viral load monitoring policies with installed lab capacity in the countries; strengthened capacity and laboratory networks for HIVDR surveillance. Among the challenges: a gap of approximately 500,000 people without ART to achieve the second "90%" target with significant ART coverage gaps in some countries; still high number of treatment regimens in some countries, especially for second line; limited treatment optimization in children with HIV[1] (phase out of obsolete drugs and formulations; introduction of new paediatric ARVs, FDC, dispersible and scored tablets); gaps in viral load coverage in some countries; and, increasing pre-treatment resistance to NNRTIs.

The new 2016 WHO recommendations[2] and the latest scientific evidence[3,4] support the inclusion of DTG-based alternative first-line regimens in national treatment guidelines (due to its high potency and genetic barrier, superiority in viral suppression, immunological recovery and retention in treatment vs. efavirenz 600 mg (EFV600), once daily dosing and good tolerability profile, low potential for drug interactions), also considering the perspective of availability of low cost generics and fixed- dose combinations (FDC) – WHO prequalified or approved by stringent regulatory authority – in particular for countries without patent restrictions. However, there are some pending issues related to safety and effectiveness in TB-HIV co-infection (including need for dose adjustment to twice daily), pregnant women and children <6 years. **Since the meeting in Brasilia, WHO released a technical update on transition to new antiretrovirals in HIV programs[5] to promote the adoption of regimens with high potency, lower toxicity, high genetic barriers to resistance, usefulness across different populations and lower cost. The use of optimized drug regimens can improve the durability of the treatment and quality of care of people living with HIV.**

Considering the regional challenge of increasing pre-treatment NNRTI resistance **(see new WHO HIVDR report released in July 2017[6])**, the directionalities of the new WHO guidelines on the public health response to pre-treatment HIV drug resistance were presented and discussed; in particular, the recommendation that countries in which the prevalence of pre-treatment DR to NNRTIs among people initiating first- line ART, regardless of previous ARV drug exposure, is ≥10% should urgently consider an alternative first-line ART regimen that does not contain NNRTIs (as defined in the 2016 WHO consolidated ARV guidelines). The preferred alternative first- line regimen in adult is DTG-based.

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[1] IATT paediatric ARV formulary and limited-use list: 2016 update. Policy brief. http://www.who.int/hiv/pub/paediatric/iatt-paediatric-hiv-2016/en/

[2] WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. Second edition. 2016. http://www.who.int/hiv/pub/arv/arv-2016/en/

[3] Jiang et al. AIDS Res Ther (2016) 13:30. DOI 10.1186/s12981-016-0115-x. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5016965/

[4] Patel et al. PLoS ONE 9(9): e105653. doi:10.1371/journal.pone.0105653 http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0105653

[5] WHO. Transition to new antiretrovirals in HIV programmes. Technical update. 2017. http://www.who.int/hiv/pub/toolkits/transition-to-new-arv-technical-update/en/

[6] WHO. HIV drug resistance report 2017. http://www.who.int/hiv/pub/drugresistance/hivdr-report-2017/en/

Since the meeting in Brasilia, WHO released the final version of the guidelines on the public health response to pre-treatment HIV drug resistance[7].

In addition, modelling exercises and estimates of projected costs across different scenarios were presented and discussed. A model developed for generalized epidemic contexts in sub-Saharan Africa[8] showed that introducing the policy of starting DTG-based first-line therapy is the most cost-effective intervention (3 interventions were considered: 1) start with EFV containing regimens; 2) start with DTG containing regimens; 3) 1st line based on pre- ART genotyping test) at any given level of pre-treatment resistance, if DTG is available at a price of 44US$/person-year. The same model adapted to upper middle income (UMIC) context shows that the cost-effectiveness of these 3 interventions varies depending on the pre-ART resistance level and the cost of DTG. These models are useful to guide the discussion, but for in-country decision making, it is necessary to adapt them to the specificities of each country. The initial and projected cost analysis of these 3 interventions in LAC was also presented. The economic impact of the introduction of DTG when the country is eligible for the access price (44US $/person-year) is minimum.

The MPP presented in details the global initiative to promote access to quality medicines in developing countries and current licenses aimed at safeguarding public health approach through negotiation with patent holders, including the specific license for access to DTG through nine generic drug manufacturers at a more affordable price (44US$/person-year). MEDSPAL (www.medspal.org) is an online database that includes the up to date status of existing patents in each country. Based on the situation analysis conducted in preparation for the meeting, LAC countries can be classified into 3 groups (Table 1).

Table 1. Classification of countries in the region based on licenses and patent protection for DTG.

Countries included in MPP license that can procure generic DTG at access price	**Countries, not included in MPP license, that cannot procure generic DTG due to patent protection or data exclusivity**	**Countries, not included in MPP license, that may benefit from MPP license to procure generic DTG[1]**
Bolivia, El Salvador, Guatemala, Guyana, Haiti, Honduras, Nicaragua	Mexico, Brazil, Colombia, Trinidad and Tobago, Peru[2] and Chile[2]	All others

[1] Countries without patent granted can benefit from other clauses of the MPP license and buy from generic manufacturers even if they are not included in the territory of the license.
[2] Data Exclusivity Protection for DTG 50mg until 2018 (Source: MPP).

[7] WHO. Guidelines on the public health response to pretreatment HIV drug resistance. 2017. http://www.who.int/hiv/pub/guidelines/hivdr-guidelines-2017/en/
[8] Phillips A et al. Cost-effectiveness of public-health policy options in the presence of pretreatment NNRTI drug resistance in sub-Saharan Africa: a modelling study. The Lancet, 2017. [Epub ahead of print] Available at: http://www.sciencedirect.com/science/article/pii/S235230181730190X?via%3Dihub

Since the meeting, DTG 50mg was included in the WHO Essential Medicines List 2017[9] and the list of products available through the PAHO Strategic Fund was updated accordingly.[10] The price agreement for generic DTG (either manufactured by Aurobindo or MPP's sublicensees) is ~44 US$/person-year for the 50mg tab and ~75US$ for the fixed dose combination of TDF/3TC/DTG. The fixed- dose combination of TDF/3TC/DTG is currently under review for its inclusion in the PAHO Strategic Fund list.

Table 2 below shows current status of prequalification of DTG products with WHO and US FDA (info updated Dec 2017)[11]:

ANDA 208355 USFDA 2	Dolutegravir (Sodium)	Aurobindo Pharma Ltd, Plot No 2, Maitrivihar, Ameerpet, Hyderabad, Telangana, 500 038, India	Tablet 50mg
HA634 (a)	Dolutegravir (Sodium)	ViiV Healthcare, 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom of Great Britain and Northern Ireland	Tablet, Film-coated 50mg
HA680	Dolutegravir (Sodium)	Cipla Ltd, Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai, Maharashtra, 400 013, India	Tablet, Film-coated 50mg
NDA 20-9618 USFDA 2	Dolutegravir (Sodium)/Lamivudine/Tenofovir disoproxil fumarate	Aurobindo Pharma Ltd, Unit VII, SEZ, APIIC Plot No SI, Survey No 411, 425, 434, 435 and 458, Green Industrial Park, Village Polepally, Mandal Jedcherla, District Mahaboobnagar, Andhra Pradesh, India	Tablet, Film-coated 50mg/300mg/300mg
NDA 209670 USFDA 2	Dolutegravir (Sodium)/Lamivudine/Tenofovir disoproxil fumarate	Mylan Laboratories Ltd, Plot No.564/A/22, Road No. 92, Jubilee Hills, Hyderabad, Telangana, 500096, India	Tablet, Film-coated 50mg/300mg/300mg

[9] Available at: http://www.who.int/medicines/publications/essentialmedicines/en/
[10] Available at: http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=21038&lang=en
[11] https://extranet.who.int/prequal/content/prequalified-lists/medicines

Several countries at the global level have initiated the transition to DTG, adopting different approaches (eligibility criteria, populations, national implementation/pilots). In mid-2017, 4 countries in the region have included DTG-based first line in their guidelines (either as preferred or alternative regimen): Brazil (preferred 1st line regimen), Chile, Mexico and Uruguay (Peru in process). The example of Brazil's transition process was presented and a review was made of the programmatic aspects of the transition process to new medicines, highlighting the importance of civil society participation in these processes, in collaboration with the Ministries of Health and other stakeholders.

Since the meeting in Brasilia, transition to DTG at global level has advanced and a number of documents gave been released to support the process at country level (some of them were presented in Brasilia by USAID and CHAI ahead of publication).

- **USAID**. Accelerating Access to Simpler, Safer, and More Affordable HIV Treatment Through ART Optimization. Available at: https://www.usaid.gov/sites/default/files/documents/1864/ICAP-optimize-overview-report-full-v4-508.pdf
- **CHAI**. HIV New Product Introduction Guide. Available at: http://teampata.org/wp-content/uploads/2017/10/CHAI-HIV-New-Product-Introduction-Guide_2017.pdf
- **MSF**. HIV & Opportunistic infection treatment: spotlight on access gaps. Available at: https://www.msfaccess.org/HIV-spotlight-on-access-gaps-2017

On the second day of the meeting participants were divided into groups according to the patent/license scenario (based on Table 1) to discuss the specific details of the introduction of new drugs (e.g. DTG, new paediatric ARVs, others) and to define some general guidelines (the summary of the result from the group work is included in Annex 3).

Conclusions

- The meeting demonstrated the importance of having up-to-date national data on the situation of HIV drug resistance, in particular pre-treatment resistance, for decision-making in terms of ART guidelines update and revision of preferred ART regimens, especially in the light of emerging NNRTI resistance.
- It reinforced the commitment of countries to establish national strategies to monitor HIV resistance (e.g. Chile, Uruguay, Paraguay, Ecuador, Dominican Republic, Barbados, etc.). Support from PAHO, regional partners and HIV ResNet lab network is available to countries in LAC for the implementation of HIVDR surveillance.
- The increase in resistance to NNRTIs was recognized as an acceleration factor for the transition to DTG, however some countries recognized that the transition is also due to a proven superiority of the DTG- vs. EFV600-based regimens.
- In the context of high pre-treatment drug resistance to NNRTIs (> 10%), the most viable scenario is to adopt a first-line regimen that does not include NNRTIs, being DTG the preferred ARV to be used in adults and adolescents (new WHO consolidated guidelines).
- One important decision factor in relation to the transition to DTG in LAC region is price, especially for countries with patent protection that currently do not have access to generic DTG formulations. In Brazil, bilateral price negotiation with different manufacturers of INSTIs was successful adopted as a strategy to reduce the price of DTG.
- The scenario of performing pre-ART genotyping was discussed and almost unanimously considered not feasible at this point in time, since laboratory capacity is limited even in countries with greater resources and with more developed laboratory networks.
- Some countries expressed concrete intentions to begin the transition process in 2017/2018 (Guatemala, Haiti, the Dominican Republic, Argentina and Cuba if access to the low cost generic DTG formulations will be confirmed based on the MPP license and its indirect coverage in countries not included in the list).
- Based on the experience from the Treatment 2.0 initiative (treatment optimization and transition to EFV-containing FDCs) and the results of the consultation, PAHO will develop a short guidance to support the process of introduction of new ARVs and transition to new preferred regimens, including DTG-based ones in light of emerging NNRTI resistance.
- The Horizontal Technical Cooperation Group should be revitalized as a space for South-South Cooperation to share experiences, good practices and lessons learnt and resources (e.g. HIVDR surveillance; DTG transition, among others).

Annex 1 – Concept Note

Introduction

Since 2012, the WHO/UNAIDS Treatment 2.0 initiative was introduced, discussed and adapted to the context of Latin America and the Caribbean (LAC) and countries have been gradually adopting it to expand access to care and antiretroviral treatment (ART) services for people living with HIV with a strong public health approach. The Treatment 2.0 ART optimization component was driven by principles of rational use of ARV medicines, simplification and standardization of regimens across different populations (e.g. use of WHO preferred regimens for first and second line), revision of national guidelines according to most recent scientific evidence and global WHO recommendations, and innovation in terms of drug selection (e.g. phase out of obsolete and non-recommended drugs) and use of fixed dose combination (FDC) to promote better adherence. In addition, thanks to an increasing access to and use of generic ARV medicines, the cost of antiretroviral treatment (per person/year) has significantly declined overtime, an countries have been able to promote a more rapid and sustainable scale up ART. In this context, the PAHO Strategic Fund has been instrumental in providing technical cooperation to strengthen supply chain management systems and processes, and providing a regional platform for pooled procurement that generated significant savings for many countries in LAC. Furthermore, the frequency and severity of ARV stock-outs declined in many countries ensuring uninterrupted access to treatment. In the post 2015, the new regional care and treatment targets (90-90-90) - aligned with global UNAIDS Fast Track and new WHO HIV Health Sector Strategy - pose new challenges for the effective, efficient and sustainable expansion of ART programs in LAC. At the same time ART programs face the challenge to introduce new technologies, based on scientific evidence based international recommendations, and innovate their response for improved effectiveness and impact on the HIV epidemic.

Integrase Strand Transfer Inhibitors (INSTI) are currently included as standard of care and preferred option for first line treatment in many international reference guidelines (e.g. IAS, DHHS, EACS), and in 2016, the new WHO recommendations on the use of antiretrovirals for treatment and prevention of HIV for the first time introduce dolutegravir (DTG), an INSTI, as alternative drug for first line regimens (1). From the systematic review performed in preparation of the WHO consolidated guidelines, a network metanalysis showed moderate-quality evidence that two NRTIs + INSTI was more effective (with higher viral suppression and CD4 cell recovery rates and lower risk of treatment discontinuation) than two NRTIs + efavirenz (EFV) at the standard dose of 600 mg/day in ART-naive adults. DTG has a comparable effect to that of raltegravir (RAL), but better than that of elvitegravir (EVG) + cobicistat in terms of viral suppression and treatment discontinuation, in addition to other clinical and programmatic advantages, including lower potential for drug interactions, a shorter median time to viral suppression and a higher genetic resistance barrier when compared with EFV. However, safety and efficacy data on the use of DTG in important populations as pregnant women, people with HIV/TB coinfection and adolescents younger than 12 years of age are not yet available (1). More recently, some evidence of higher than expected proportion of discontinuation of DTG based regimens due to CNS side effects compared to clinical trials is emerging from real life settings (2). Therefore, ensuring close monitoring of adverse events through active toxicity

surveillance strategies is a critical component in view of the possible adoption of DTG in preferred first line regimens and should be considered in its programmatic implementation.

At the time of preparation of this concept note, DTG was not included in the WHO Essential Medicines List (EML), but was submitted to the review committee in March 2017. The following products are currently available in the market:

- TIVICAY (dolutegravir tab 50 mg) by ViiV Healthcare UK Limited (Glaxo) (FDA approved; WHO PQ 14/Oct 2014)
- TRIUMEQ (dolutegravir, abacavir, lamivudine tab 50/600/300 mg) by ViiV Healthcare UK Limited (Glaxo) (FDA approved)
- Dolutegravir (tab 50 mg) by Aurobindo (tentative FDA approval and pending WHO PQ; currently included in Global Fund ARV list).

In LAC, access to DTG formulations is still limited. In 2016, Brazil announced that the Ministry of Health included DTG in their national guidelines as preferred drug for persons with HIV initiating antiretroviral treatment in the public sector, estimating to reach around 100,000 people on use of this medication by end of 2017. Through direct negotiation with the originator (ViiV Healthcare), Brazil obtained a price reduction from US$ 5,1 to US$ 1,5 per tablet of DTG.[12] Other LMICs as Botswana, Kenya, Nigeria and Uganda are also introducing DTG in their national ARV formularies in 2017. As of September 2016, DTG production has also been sub-licensed to several generic pharmaceutical companies (Cipla, Desano, Emcure, Hetero Labs, Laurus Labs, Lupin, Micro Labs, Mylan and Strides). The following LAC countries are included in the Medicine Patent Pool license to waive DTG patent and be able to access generic DTG formulations at low prices (approx. 44 US$ per person per year): Bolivia, El Salvador, Guatemala, Guyana, Haiti, Honduras, Nicaragua.[13] On the other hand, additional countries in LAC region could procure generic DTG outside license because of the absence of specific patent protection. Only Brazil, Colombia and Mexico are not allowed to buy generics according to "MedsPal". Although in the pipeline, generic and more affordable fixed dose combinations of DTG are not yet commercialized and likely to be available in 2018, and the current generic products are not widely available for middle income countries due to patent protection in those settings.

As detected at global level, an increase in pre-treatment HIV drug resistance to non-nucleoside analogues (NNRTI) has been observed in LAC (3), recently confirmed by few nationally representative pre-treatment drug resistance (PDR) surveys implemented in Argentina and Mexico using WHO recommended approach (4,5), as well as preliminary and still unpublished data from other ongoing surveys (e.g. Guatemala). In such cases of countries with important levels of PDR to NNRTI (e.g. 10%), an accelerated transition from NNRTI-based to INSTI-based first line ART may be warranted. WHO is coordinating the development of a new set of evidence based recommendations for the management of HIVDR from a public health perspective in countries facing increasing levels of PDR to NNRTI, which will

[12] http://www.brasil.gov.br/saude/2016/09/sus-oferece-melhor-tratamento-do-mundo-para-pacientes-com-hiv-aids

[13] http://www.medicinespatentpool.org/viiv-mpp_extend-licence-for-dtg-in-all-lower-mics/ http://www.medicinespatentpool.org/mpp-licences-on-dolutegravir-dtg-2/

provide additional inputs for decision-making in relation to transitioning from EFV- to DTG-based first line regimens, or introducing routine pre-treatment HIV genotyping to assess individual eligibility for DTG based on NNRTI PDR.

In conclusion and based on current scientific evidence, the introduction of DTG-based first line regimens offer an opportunity for improved treatment outcomes in terms of retention, viral suppression, and CD4 cell recovery; on the other hand additional evidence is needed on its safety and efficacy in certain populations and DTG-based FDC are not yet available. The decision and timing of introducing DTG in national ART guidelines and formularies in countries in LAC will require accurate considerations of feasibility and cost-effectiveness scenarios based on a number of factors, among which the most important are:

a) the evidence of high levels of NNRTI resistance which would justify an accelerated process of transition from NNRTI-based first-line regimens to DTG-based ones;
b) the availability and price of the product (access price for DTG in selected countries vs. negotiated directly with the manufacturer either on a country by country basis or through joint negotiation and pooled procurement mechanisms);
c) the lab capacity and associated costs of performing a high throughput of HIV genotyping to initiate DTG selectively in individuals with pre-treatment resistance to NNRTI.

In addition, the transition from NNRTI- to INSTI-based regimens from a programmatic perspective will require careful planning at country level in terms of normative framework, supply chain management systems and processes, pharmacovigilance and active monitoring of adverse events, training of human resources and social communication strategies, among most important component of the transition. The experience of the Treatment 2.0 Initiative and the transition plans to WHO-preferred regimens will provide an important background “know how” to guide this new process of transition from NNRTI- to INSTI-based regimens.

Based on these key factors, and considering the perspective of paradigm change in ART guidelines that is occurring at global level, this consultation with country representatives and key partners aims at discussing and identifying most feasible, cost-effective and coordinated strategies for countries in Latin America and the Caribbean to optimize antiretroviral treatment and access dolutegravir, minimizing the impact on the sustainability of universal care and treatment programs.

Main objective

- Discuss with Latin American and Caribbean countries and key partners opportunities and technical cooperation needs for treatment optimization and transition to dolutegravir-based 1st line ART, prioritizing countries with evidence of higher levels of pre-treatment resistance to NNRTIs, and based on WHO recommendations for ART and HIVDR management and other feasibility and cost-effectiveness analysis.

Specific objectives:

- Present WHO guidelines on ART, including new scientific evidence on the use of DTG for first-line treatment, and their implications for HIV treatment optimization and guideline update.
- Present regional data on HIV pre-treatment drug resistance and discuss their potential impact on effectiveness of current EFV-based preferred regimens and feasibility of possible public health actions (e.g. transition to DTG-based first line vs. use of pre-treatment HIV genotyping in treatment naive patients to identify individuals with NNRTI resistance).
- Present new WHO protocols for HIVDR management and discuss their relevance and use in the LAC region.
- Present current market landscape to access DTG at global level and in LAC region and discuss procurement strategies for the region based on a tiered approach (MPP license countries vs. others).
- Share country experiences of programmatic implementation of the NNRTI-INSTI transition, in particular the experience of Brazil.
- Discuss the programmatic implementation of the NNRTI-INSTI transition, including active monitoring of adverse events and implementation of pregnancy ARV registry for persons with HIV using DTG containing regimens to be implemented in LAC.
- Discuss and define agreed upon strategies to accelerate access to DTG in priority countries with higher levels of NNRTI PDR and based on a tiered approach.

Expected results

Strategies and technical cooperation needs to advance in optimization of antiretroviral treatment programs and the access to DTG in LAC discussed and identified with Latin America and the Caribbean countries and key partners.

Participants:

- Representatives from 25 Latin American and Caribbean countries
- PAHO/WHO (country office, regional, subregional advisers and WHO/HQ)
- Invited partners: UNAIDS, UNITAID, MPP, PEPFAR/USAID/CDC, Global Fund, PANCAP, Fundación Huesped.
- Representatives from civil society organizations (ABIA, REDBOL, AIS Guatemala, AIS LATCA, JAS)

References

(1) WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed. WHO, Geneva, 2016.
(2) De Boer M et al. Intolerance of dolutegravir containing cART regimens in real life clinical practice.AIDS, online edition. DOI: 10.1097/QAD.0000000000001279 (2016).
(3) Avila-Rios S, Sued O, Rhee SY et al.Surveillance of HIV Transmitted Drug Resistance in Latin America and the Caribbean: A Systematic Review and Meta-Analysis. PLoS One. 2016 Jun 29;11(6):e0158560. doi: 10.1371/journal.pone.0158560.
(4) Bissio E, Barbás MG, Bouzas MB, et al. Pretreatment HIV-1 drug resistance in Argentina: results from a surveillance study performed according to WHO-proposed new methodology in 2014-15. J Antimicrob Chemother. 2016 Oct 26. pii: dkw445. [Epub ahead of print]
(5) Ávila-Ríos S, García-Morales C, Matías-Florentino M, et al. Pretreatment HIV-drug resistance in Mexico and its impact on the effectiveness of first-line antiretroviral therapy: a nationally representative 2015 WHO survey. Lancet HIV. 2016 Dec;3(12):e579-e591. doi: 10.1016/S2352-3018(16)30119-9.

Annex 2 - Agenda

Day 1 – 6th June 2017

8:00-8:30	Registration of participants	
Morning sessions. Chair persons: Pedro Cahn (Argentina), Adele Benzaken (Brazil) Rapporteurs: Marcelo Vila; Pedro Avedillo		
8:30-8:45	• Opening remarks	• PAHO • UNAIDS • MOH Brazil
8:45-9:00	• Review of objectives and agenda • Introduction of participants	• Romina Oliveira (PAHO)
9:00-9:30	**Session 1 – The regional context in Latin America and the Caribbean** • Progress and challenges for the optimization and expansion of effective antiretroviral treatment in Latin America and the Caribbean (20') Q/A (10')	• Giovanni Ravasi (PAHO)
09:30-11:00	**Session 2 – New WHO global guidelines and update on scientific evidence** • Alternatives for NNRTI based first line regimens: an update from recent and ongoing clinical trials (20') • WHO guidelines, new evidence on use of DTG for first-line and clinical and programmatic implications (20') • WHO guidelines on the public health management of HIV drug resistance (20') Q/A (30')	• Pedro Cahn (Argentina) • Marco Vitoria (WHO) • Nazle Veras (Brazil)
11:00-11:30	Coffee break	
11:30-13:00	**Session 3 – Decision making based on modeling and feasibility** • Modelling of public health policy options when pre-treatment NNRTI drug resistance is high: cost-effectiveness and threshold considerations (20') • Cost projections of different scenarios in LAC (20') • Considerations on scaling up lab capacity for pre-treatment HIV genotyping (20') Q/A (30')	• Giovanni Ravasi (PAHO) on behalf of Andrew Phillips (UK) • Manuel Lavayen (PAHO) • Ana Flavia Pires (Brazil)
13:00-14:00	Lunch	

Cont.

Afternoon sessions. Chair persons: Giovanni Ravasi (PAHO), Felipe Carvalho (Brazil) *Rapporteurs: Bertha Gómez; Sandra Jones*		
14:00-15:00	**Session 4 – Access to DTG: current landscape** • Global scenario, challenges and opportunities for LAC countries (20') • Regional scenario and the role of the PAHO Strategic Fund (20') Q/A (20')	• Erika Duenas (MPP) • Manuel Lavayen (PAHO)
15:00-16:30	**Session 5 – Programmatic guidance for the transition to DTG** • Guidance for transition to DTG: considerations for countries (10') • Country experiences (20'each): ▪ Brazil ▪ CHAI experience ▪ USAID experience (webex tbc) Q/A (20')	• Marco Vitoria (WHO) • Brazil (Adele Benzaken) • Carolyn Amole (CHAI) • Meghan Majorowski (USAID)
16:30:16:45	• Instructions on the Facilitated Group Work for Day 2 • Closing	

Cont.

Day 2 – 7th June 2017

Morning sessions. Chair persons: Marco Vitoria (WHO), Anton Best (Barbados)		
8:30-10:30	**Session 6 – Facilitated group work (4 groups)**	
10:30-11:00	Coffee break	
11:00-12:00	**Plenary session and group work presentations** Presentations (10'each group) Moderated discussion (20')	
12:00-12:45	**Session 7 – Summary of meeting and next steps** Presentation of main outcomes from discussion and group work to define next steps for optimization and DTG transition (30') Q/A (15')	• Rapporteurs
12:45-13:00	Closure (15')	• PAHO • UNAIDS • MOH Brazil
13:00-14:00	Lunch	

Annex 3 – Group work summary

HIVDR surveillance, NNRTI resistance and HIV genotyping capacity for decision making about transition to DTG.

"*Countries with evidence of >10% of NNRTI pre-treatment drug resistance (PDR) should urgently consider using an* ***alternative first-line regimen that does not contain an NNRTI*** *according to current WHO guidelines (****Annex 1****). Where using an alternative non-NNRTI regimen is not possible to implement at the population level, countries can consider using pre-treatment genotype resistance testing to guide first line treatment regimen selection and continued viral load monitoring as per the current WHO guidelines*".

Results of group work in the table below by groups of countries

GROUP 1	GROUP 2	GROUP 3a	GROUP 3b
Countries included in MPP license that can procure generic DTG	Countries, not included in MPP license, that cannot procure generic DTG due to patent protection or data exclusivity	Countries, not included in MPP license, that may benefit from MPP license to procure generic DTG[1]	Countries, not included in MPP license, that may benefit from MPP license to procure generic DTG[1]
Bolivia (civil society), Guatemala (MOH and civil society), Haiti (Government and USAID), Nicaragua	Mexico, Brazil (MOH and civil society), Peru (MOH and civil society) and Chile	Argentina, Costa Rica, Cuba, Ecuador, Paraguay, Uruguay, Dominican Republic, Panama	Jamaica (civil society), Barbados, Bahamas, CDC
• Agreement with the statement, although not all countries have recent pre-treatment drug resistance data (only GTM and NIC, although HAI is planning in 2017) to make an informed decision at this point in time. • Transition to DTG could be considered,	• Only Mexico and Brazil have recent HIVDR data, although Chile is aiming at implementing HIVDR surveillance with support from PAHO. • Regardless of availability of recent drug resistance data, countries should advance to expand access to integrase inhibitors, but the	• In agreement with the statement, if DTG will be available at access price (44$ person-year). • Only Argentina has recent data (>10% NNRTI PDR), Cuba has preliminary data (>15%) and some data (no WHO recommended protocol) in Panama (9,7%).	• In agreement with the statement, although not all countries have recent HIVDR data to take decision. • Jamaica has some recent data (>10% - although not based on WHO protocol – WHO survey ongoing). Barbados is planning. No data for Bahamas. • HIVDR surveillance should be prioritized

regardless of availability of resistance results because of superiority of the drug and cost effectiveness modeling (when DTG is available at 44US$) (HAI and Bolivia – civil society) • In any case HIVDR surveillance should be implemented to have a baseline and generate data to inform ARV selection and regimen updates. • Lab capacity for pre- treatment HIV genotyping for clinical purpose (not surveillance) limited or not in place. **Country information** • Guatemala (NNRTI PDR >10%) confirmed interest in moving forward with transition soon. • Nicaragua (NNRTI PDR >10%) may also, but after review of HIVDR data with their expert committee to take a decision about alternative non-NNRTI regimen • Haiti (pending PDR survey result, although interested	decision and the selection of which integrase inhibitors will be based on budget assessment in any individual countries. • General agreement on the importance to strengthen HIVDR surveillance in countries, including regional collaborations (networks). • Pre-treatment HIV genotyping for clinical purpose (not surveillance) would not be feasible in the short term (Peru and Chile); targeted (by region or specific populations) in Brazil and Mexico. **Country information** • Brazil planning to expand transition to TLD for persons currently on TLE. • Mexico (NNRTI resistance >10% at national level) planning a subnationally representative HIVDR survey to identify different patterns of resistance and adapt policies to local situation. Also considering use of elvitegravir FDC as preferred or alternative first line	• HIVDR surveillance should be prioritized to generate data for decision making – countries could also consider using results from neighboring countries. • Most countries report plans to implement surveillance in the near future. • Pre-treatment HIV genotyping for clinical purpose (not surveillance) would not be feasible. • HIV genotyping test should be more affordable **Country information** Most countries interested in considering DTG, if available at access price benefitting from the “effective coverage” of the MPP license (in particular ARG, DOM, CUB).	at this point time to assess NNRTI PDR and the urgency of transition. • Nevertheless, considering the superiority of DTG (vs. EFV) and the future availability of PQ generics and FDC, transition to DTG will occur regardless of PDR results. • Regional lab capacity for pre- treatment HIV genotyping for clinical purpose (not surveillance) is limited and resistance testing for surveillance purpose and clinical monitoring at treatment failure should be prioritized. **Country information** • Barbados is paying DTG at 600US per person per month. Caribbean countries may be interested in considering DTG, if available at access price benefitting from the “effective coverage” of the MPP license (to be further discussed at subregional level considering the limited participation of Caribbean countries in the meeting).

in considering transition regardless).	regimen (cost is equivalent to TEE/TLE and significantly cheaper than DTG-based one which is approximately 3000$ per person-year). • Chile has included RAL, DTG and EVG/cob in the draft of the new ART guidelines, but currently being reviewed to try to improve public health approach to ARV regimens – data exclusivity protection expiring in 2018 may enable a transition to DTG in the future. • For Chile and Mexico, a current strategy could be creating competence among manufacturers of different INSTI to reduce price (e.g. of Brazil with RAL vs. DTG).		

PART B - Actions to be taken at country level by key programmatic area for the process of treatment optimization, introduction and transition to new ARVs

Programmatic area	Group 1	Group 2	Group 3a	Group 3b

Regulation	• Update national EML • Update national guidelines/protocols • Ensure registration of products (TC needed)	• Technical support to facilitate registration of generic in short term • Compulsory license could be a feasible mechanism in some cases	• Update national formulary with new ARVs • Registration of generics	• Review regulatory barriers in countries (TC needed PAHO/MPP) • Registration of products or manufacturers (depending on countries)
Procurement and supply management	• Develop a structured transition plan with criteria and avoiding stock wastage (TC needed)	• Pooled procurement via Strategic Fund (MERCOSUR) • Consolidate regional demand for innovator drugs • Address transition of pediatric ARVs • Regional price database (PAHO) • PAHO advocacy with Pharma on ceiling price for drugs (preferred drugs) • Strategic Fund to access ARVs with expiring patents • Generate dialogue with scientific organizations about quality of generic drugs acquired through the SF	• Estimate the number of people that will use DTG. • Pooled procurement via PAHO Strategic Fund to reduce price and make transition sustainable • Implementation of transition plan (TC needed)	• Supply chain management assessments to improve efficiency (TC PAHO, USAID) • Consider pooled procurement where appropriate
Normative framework	• Update national guidelines/protocols (TC needed) • Harmonization with all ART providers at national level (e.g. social security).	• Update national guidelines/protocols and promote GRADE approach	• Update ART guidelines based on results of HIVDR surveillance (challenge for countries that have recently updated their guidelines)	Review and update of national guidelines (TC PAHO and CDC)
Human resources	• Capacity building	• Ongoing training	• Training	• Training in

	(training/retraining) of health providers and professionals involved in SCM (TC needed).	of human resources (providers and lab personnel), including e-training and other IT-based approaches • Applications for providers and patients • WHO service delivery model to be discussed and promoted with scientific organizations		clinical management of HIV and supply chain management.
Pharmacovigilance/ Adverse event monitoring	• Strengthen pharmacovigilance of ARVs • Implement information systems or adapt current ones to capture data on AEs in persons on ART (linked to medical history).	• Sentinel pharmacovigilance for new drugs • Start with pilot (specific ARV and then expand) • Training of providers on adverse events	• Implement a PV system – active PV for ARV • Standardized data collection for PV and AEs monitoring in countries that don't have it	• Assessment of PV capacity and identify actions to strengthen (information systems, human resources, processes, etc.) (PAHO, PEPFAR)
Social communication	• Involvement of all stakeholders in the decision-making process of transition and subsequent communication strategies (as part of the national response towards 90-90-90).	• Advocacy of civil society for introduction of new drugs (caveat, possible pressure of Pharma on some NGOs). • Ensure participation of civil society in decision making processes • National campaigns and social spaces for health messaging	• Civil society participation	• Social marketing is very important to expand access to services across the HIV continuum. • The involvement of civil society is critical in this process. • Innovation (e.g. new ARV drugs) should be addressed at

				both levels of treatment literacy (individual) and public fora (e.g. advocacy, social communication campaign, etc.)