WHO 2019指南更新解读

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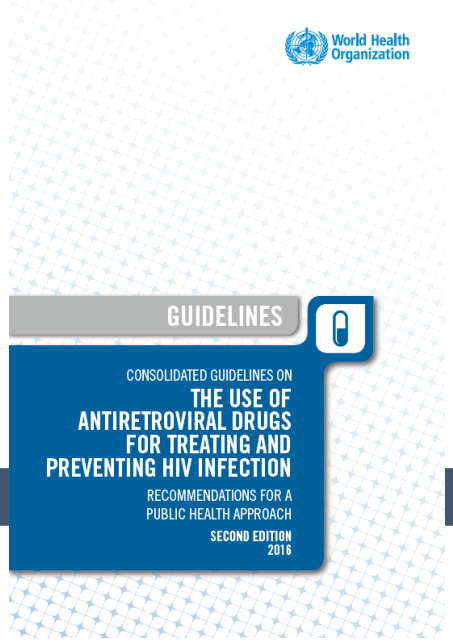
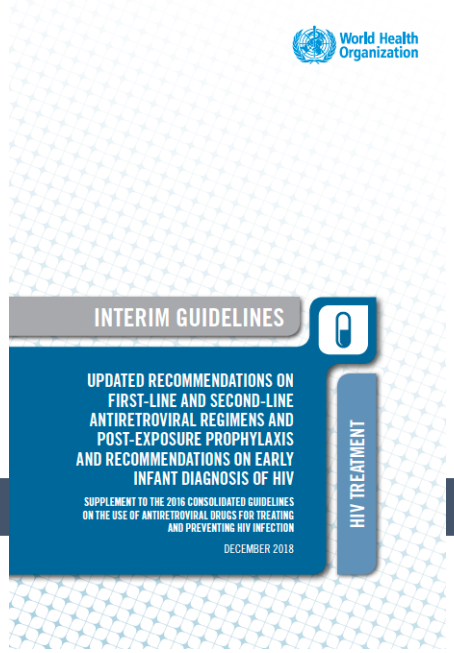
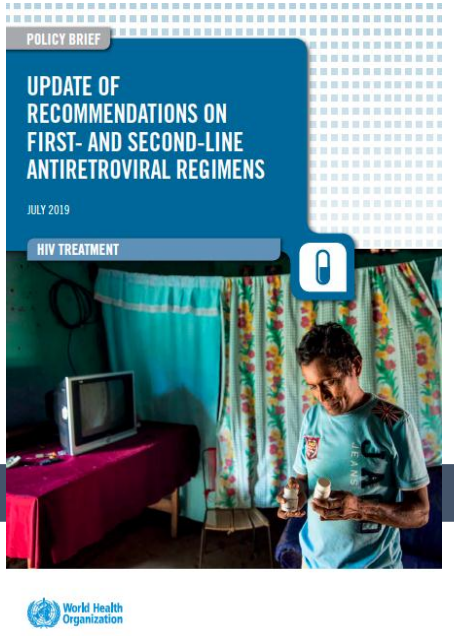
背景：WHO 2019HIV治疗指南更新



2016年版：
以EFV 600mg为首选一线方案；
以ATV/r或LPV/r为首选二线方案



2018年版：
以DTG为初治首选一线方案；
以DTG+NRTIs骨干药物为非-DTG方案失败者的首选二线方案



2019年版：
以DTG为全人群首选一线和二线方案

初治一线方案推荐

WHO 2019指南：一线ART方案推荐

一线ART方案推荐意见	相比2018年版更新点
1. 推荐**多替拉韦 (DTG)**联合核苷类反转录酶抑制剂（NRTI）骨干药物为HIV感染者启动ART的**首选一线方案** ✓ 成人及青少年【强推荐，中等确定性证据】 ✓ 获批DTG剂量的新生儿及儿童【附条件推荐，低确定性证据】	• **适用人群扩展**：“成人及青少年”包含孕妇、育龄期女性、合并TB者等全人群 • “成人及青少年”人群**推荐强度增强**：附条件推荐 → 强推荐
2.推荐低剂量依非韦伦（EFV 400mg）联合NRTI骨干药物为成人及青少年HIV感染者启动ART的备选一线方案（对EFV/奈韦拉平（NVP）治疗前耐药超过10%者除外）【强推荐，中等确定性证据】	• 新增推荐
3.推荐以拉替拉韦（RAL）为基础的方案为未获批DTG剂量的新生儿及儿童的备选一线方案【附条件推荐，低确定性证据】	\
4.推荐以RAL为基础的方案为新生儿首选一线方案【附条件推荐，极低确定性证据】	\

注：

DTG被批准用于6岁以上体重超过15kg的儿童，体重20kg及以上儿童可服用分散的50mg成人药片

体重20kg以下儿童的DTG剂量有望2019年晚期获批，儿童可分散药片也在发展，有望2020年中期实现

8. Update of recommendations on first- and second-line antiretroviral regimens. Geneva, Switzerland: World Health Organization; 2019(WHO/CDS/HIV/19.15).Licence: CC BY-NC-SA 3.0 IGO.

人群	首选一线方案	备选一线方案	特殊情境
成人及青少年	TDF + 3TC (or FTC) + DTG[a]	TDF + 3TC + EFV 400 mg[b] ~~删去2018临时指南中“TDF + 3TC (或FTC) + EFV600mg”方案~~	TDF + 3TC (or FTC) + EFV 600 mg[b] AZT + 3TC + EFV 600 mg[b] TDF + 3TC (or FTC) + PI/r[b] TDF + 3TC (or FTC) + RAL TAF[c] + 3TC (or FTC) + DTG ABC + 3TC + DTG[a]
儿童	ABC + 3TC + DTG[d]	ABC + 3TC + LPV/r ABC + 3TC + RAL[e] TAF + 3TC (or FTC) + DTG[f]	ABC + 3TC + EFV (or NVP) AZT + 3TC + EFV[g] (or NVP) AZT + 3TC + LPV/r (or RAL)
新生儿	AZT + 3TC + RAL[h]	AZT + 3TC + NVP	AZT + 3TC + LPV/r[i]

2018版基础上删除

2018版基础上新增

[a]为育龄期女性提供有效避孕措施。可向希望怀孕或未能获得有效避孕措施且已充分了解新生儿神经管缺陷风险可能增加的育龄期女性开具DTG处方（从怀孕到前三个月结束）。确认怀孕三个月以上者，应在怀孕期间启动或继续使用DTG

[b]基于EFV的ART不应用于EFV治疗前耐药评估风险>=10%的国家。基于DTG的ART为首选，若DTG不可用，则应使用增强型PI方案。PI/r的选择取决于方案特征

[c]确诊骨质疏松症和/或肾功能损害者可考虑使用TAF

[d]适用于获批DTG剂量的年龄与体重组

[e]仅当LPV/r不可用时方使用RAL为备选方案

[f]适用于获批TAF剂量的年龄与体重组

[g]EFV避免用于3岁以下儿童

[H]初始启动RAL方案的新生儿应尽快转换为LPV/r方案

[i]出生两周后可使用LPV/r糖浆或颗粒

8. Update of recommendations on first- and second-line antiretroviral regimens. Geneva, Switzerland: World Health Organization; 2019(WHO/CDS/HIV/19.15).Licence: CC BY-NC-SA 3.0 IGO.

WHO推荐DTG为首选一线方案原因

- **DTG联合两种NRTIs方案相比基于EFV的方案：**
  - **疗效及安全性**
    - ✓病毒抑制快速高效
    - ✓发生治疗中断少
    - ✓特殊人群（育龄期女性、合并TB者等）适用证据增加
  - **药物间相互作用（DDI）少**
  - **基因性耐药屏障高**
  - **成本-效益高**

1. WHO指南编写组：DTG初治疗效及治疗中断状况优于EFV

主要研究终点	DTG vs EFV_{600}	证据质量
病毒抑制（96 周）	**DTG 更好**	中等
治疗中断	**DTG 更好**	高
CD4 恢复（96 周）	**DTG 更好**	中等
死亡率	相似	低
艾滋病进展	相似	低
严重不良反应事件	相似	低

9. Steve Kanters, For WHO ARV GDG, 16-18 May 2018. WHO, 2018.

2. 孕期使用DTG：新生儿神经管缺陷患病率降低

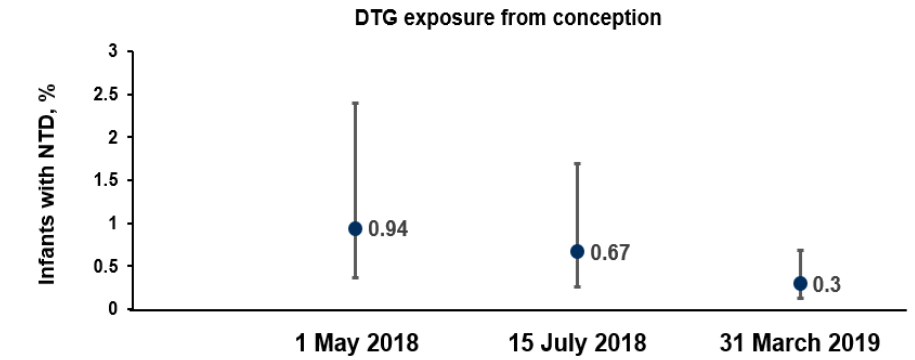
—2018年5月，对Tsepamo出生结果监测研究中偶然发现，在怀孕时接受DTG治疗的博茨瓦纳妇女的神经管畸形（NTD）发病率增加[1]:DTG vs non-DTG ART: **0.94%** (0.37% to 2.4%) vs **0.12%** (0.07% to 0.21%)

—2018年7月，世卫组织指南更新，建议将DTG + 3TC / TDF作为使用有效避孕或无生育潜力的妇女和少女的首选一线方案[5] :EFV 600 mg +（3TC或FTC）/ TDF推荐给想要怀孕或未怀孕有效避孕的女性和青春期少女

—2019年3月分析中，接受DTG治疗的女性患NTD患病率低于最初数据，但仍略高于其他接触组[6]:2019年3月: **0.3%** DTG vs **0.1%** non-DTG ART; estimated difference: 0.20% to 0.27%

	Conception			Pregnancy	HIV Negative
	DTG (n = 1683)	Non-DTG (n = 14,792)	EFV (n = 7959)	DTG (n = 3840)	(n = 89,372)
Total NTDs per exposures, n/N	5/1683	15/14792	3/7959	1/3840	70/89372
▪ Prevalence difference, % (95% CI)	Ref	0.20 (0.01-0.59)	0.26 (0.07-0.66)	0.27 (0.06-0.67)	0.22 (0.05-0.62)
NTDs per exposures since May 2018, n/N	1/1275	1/3492	0/2172	1/1028	9/23,315

The prevalence rate of NTDs among new-borns whose mothers were exposed to DTG-based ART at conception decreased at each data cut[1-3]



	1 May 2018	15 July 2018	31 March 2019
Infants with defect, n	4	4	5
Exposures, n	426	596	1685
Percent with defect, (95% CI)	0.94 (0.37, 2.4)	0.67 (0.26, 1.7)	0.30 (0.13, 0.69)

1. Zash. NEJM. 2018; 379:979. 2. WHO Statement. May 2018. 3. EMA Statement. May 2018. 4. FDA. Sept 2018. 5. WHO ART. 2018. 6. Zash. IAS 2019. Abstr MOAX0105LB.

Slide credit: clinicaloptions.com

WHO 2019更新：DTG 和NTD风险提示

If the neural tube defect signal currently observed in Tsepamo study is confirmed, although it is three-times higher than the other populations, the absolute risk is very low, 0.30% – 1 in 1000 in the general population with potential increase to 3 in 1000, a risk difference of 2 excess neural tube defect per 1000 periconception exposures compared to EFV ART at conception. With recent data made available from expanded Minsitry of Health and CDC surveillance from Botswana, the weighted estimate risk remains low at 0.36% (95% CI 0.10 – 0.62).

虽然Tsepamo研究表明DTG NTD的风险是其他人群的3倍，**但绝对风险非常低**，相比受孕时使用EFV方案增加2/1000。

The risk–benefit models suggest that the benefits of DTG for women of childbearing potential newly initiating ART, which include greater maternal viral suppression, fewer maternal deaths, fewer sexual transmissions and fewer mother-to-child transmissions, are likely to outweigh the risks, such as adult morbidity resulting from DTG-associated weight gain and neonatal deaths among the infants of pregnant women with DTG-associated weight gain. DTG is also predicted to be more cost-effective, resulting in more disability-adjusted life-years averted at a lower cost than EFV.

风险 - 效益模型表明，DTG对育龄期初治ART患者的益处包括：更高的母体病毒抑制，更少的孕产妇死亡，更少的性传播和更少的母婴传播，这些益处可能超过了使用DTG风险（如 与DTG相关的体重增加带来的相关风险）。相比EFV，DTG预计也会更具成本效益，更能降低因治疗失败带来的成本。

3. 合并TB者： DTG与利福平联用疗效可、DDI少

- INSPIRING研究[12]：相比EFV，DTG 50mg每日两次用于接受含利福平治疗的合并TB者：耐受性良好，疗效相当

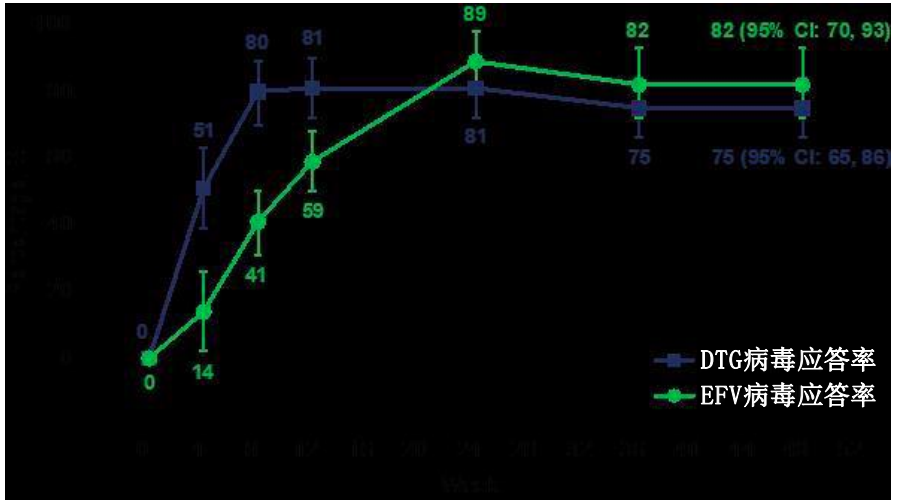
	DTG组	EFV组
48周病毒学应答率	75%（52/69）*，95% CI：65%，86%	82%（36/44），95% CI：70%，93%
死亡或转换用药	0	0
药物毒性致治疗中断	0	2
病毒学失败	2，无耐药突变	1，出现NRTI和NNRTI耐药突变

* 注：其中DTG组有5例患者因失访等非治疗性原因中断治疗，导致DTG组终点人数比例低于EFV组

Table 2. Summary of Snapshot study outcomes (plasma HIV-1 RNA < 50 c/mL), by visit, treatment group, and study population.

Arm	ITT-E 24 weeks	ITT-E 48 weeks	PP 48 weeks
Dolutegravir	56/69 (81%)	52/69 (75%)	49/62 (79%)
	95% CI 72-90%	95% CI 65-86%	95% CI 69-89%
Efavirenz	39/44 (89%)	36/44 (82%)	33/41 (80%)
	95% CI 79-98%	95% CI 70-93%	95% CI 68-93%

*ITT-E=intent-to-treat exposed; PP=per protocol



12. Dooley KE, Kaplan R, Mwelase N, Grinsztejn B, Ticona E, Lacerda M et al. Dolutegravir-based antiretroviral therapy for patients co-infected with tuberculosis and HIV: a multicenter, noncomparative, open-label, randomized trial. Clin Infect Dis. 2019 doi: 10.1093/cid/ciz256. [Epub ahead of print].

- 由于DTG与利福平的药物间相互作用（DDI），合并TB者DTG剂量需增至50mg每日两次，该剂量DTG药代动力学可[13]

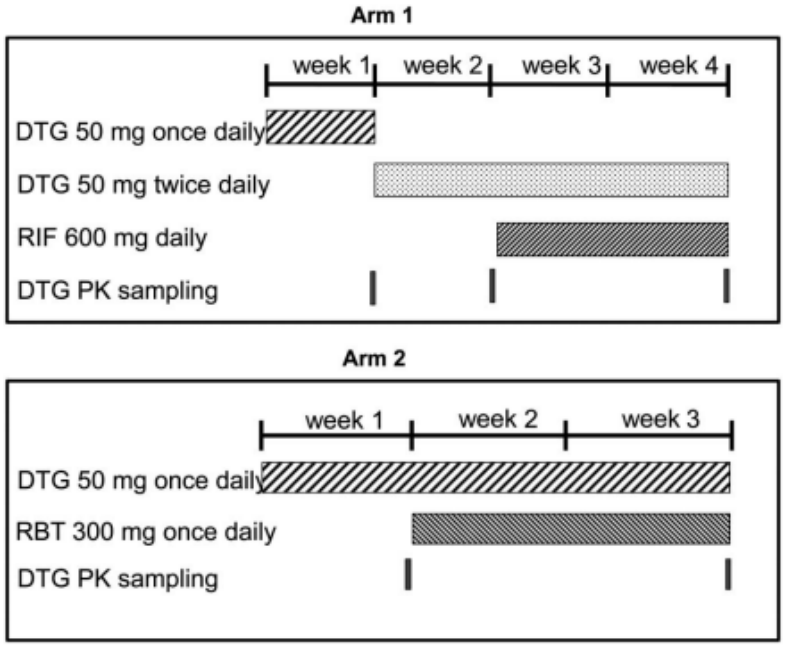
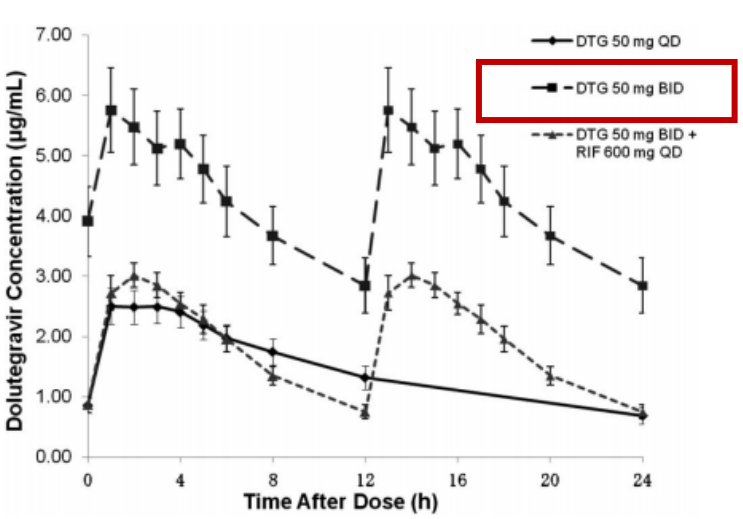
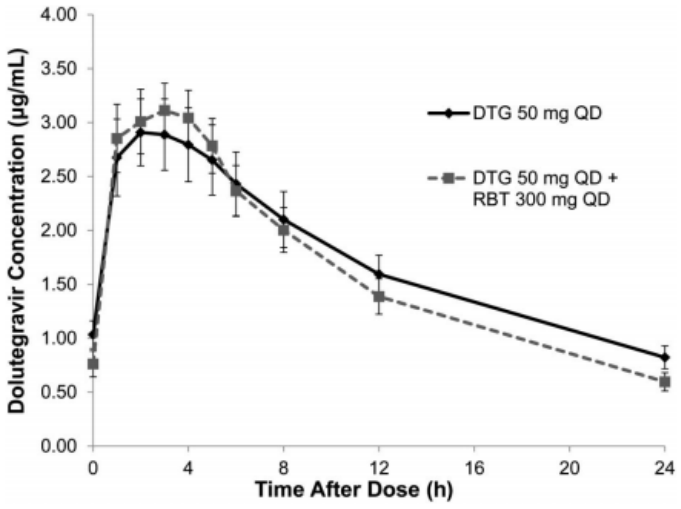


FIGURE 1. Schematic of the dosing regimen and DTG pharmacokinetic sample collection for the RIF arm (A) and the RBT arm (B).





13. Dooley KE, Sayre P, Borland J, Purdy E, Chen S, Song I et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr. 2013;62:21–7.

4. DTG相比EFV：与常见药物间相互作用少

常用药物	是否存在药物相互作用					
	DTG	RAL	EVG/c	EFV	ATV/r	DRV/r
口服避孕药	▲	▲	■	●	■	■
质子泵抑制剂	▲	▲	▲	▲	●	▲
H_2 拮抗剂 (包括 西咪替丁，法莫替丁，尼扎替丁和雷尼替丁)	▲	▲	▲	▲	■	▲
Methadone美沙酮	▲	▲	▲	■	■	■
丙型肝炎蛋白酶抑制剂 (telaprevir, boceprevir)	▲	▲	●	■	■	■
他汀类药物	▲	▲	■	■	■	■
利福平	■	■	●	■	●	●
镁/铝抗酸剂，钙和铁剂 多种维生素	■	■	■	▲	▲	▲

▲ 无相互作用

■ 潜在相互作用

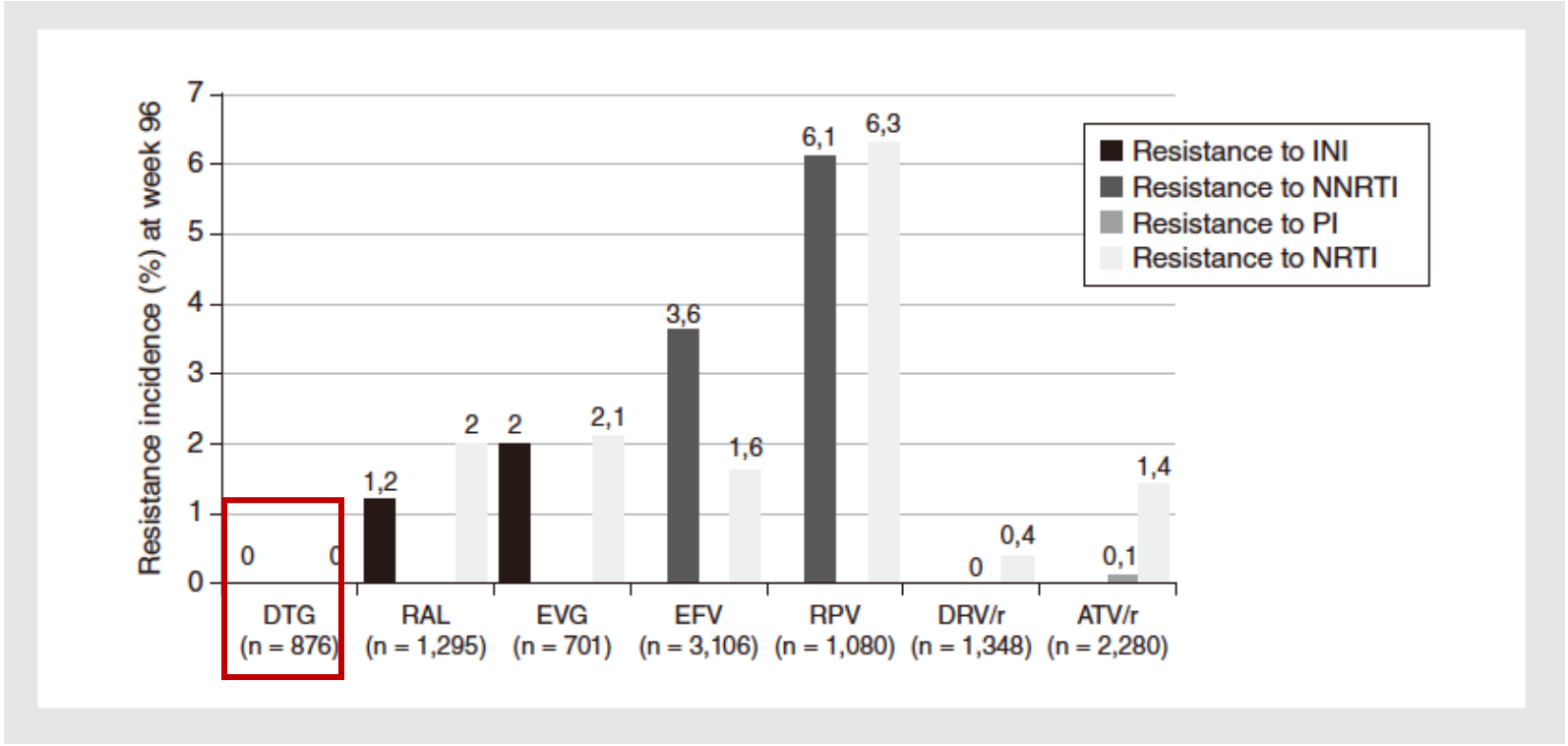
● 慎用或禁用

Reference：https://programme.aids2018.org/PAGMaterial/PPT/6583_4160/First_Second_PEP_ARV%20guidelines_Doherty_24%20July%202018_SHORT_2.pptx

5. DTG基因性耐药屏障高

- 文献综述研究：体外和体内试验均表明，DTG相对于其他整合酶抑制剂及非整合酶抑制剂类ARV药物，具有高基因性耐药屏障

初治患者第96周耐药发生率



14. Treviño A, Cabezas T, Lozano AB, García-Delgado R, Force L, Fernández-Montero JM et al. Dolutegravir for the treatment of HIV-2 infection. J Clin Virol. 2015;64:12–5.

讨论：DTG与体重管理

- Hill A等[17]开展的一项网络meta-分析显示：接受以DTG为基础的方案治疗者48周体重增加3-5kg（接受TAF+3TC+DTG方案者的体重增加最显著）【低确定性证据】
- 社区及出现DTG相关体重增加女性患者反馈：体重增加为可接受的结局
- WHO建议：启动DTG治疗的同时，可通过健康饮食、避免吸烟和规律锻炼强化体重管理

More research is needed with patient communities and advocacy groups to understand the social implications of potential weight gain. The early response from community and women enrolled in studies who experienced weight gain while taking DTG, was that weight gain is largely a viewed as a favourable outcome, but that they desired further information on the potential health implications as this becomes more available. Adequate counselling and support on the potential weight gain was clearly emphasized by the groups.

17. Hill A, Waters L, Pozniak A. Are new antiretroviral treatments increasing the risks of clinical obesity? J Virus Erad.2019;5:e45–7.

EFV 400mg：备选一线方案

EFV 400mg vs. EFV 600mg

- 一项更新的系统评价研究发现：EFV 400mg比EFV标准剂量（600mg）耐受性更好、治疗中断和严重治疗相关不良事件发生风险更低
- EFV 400mg相比EFV 600mg ：药片更小，治疗花费更少；两者均可用于固定剂量联合用药方案
- EFV 400mg与EFV 600mg一样，可安全用于孕妇：博茨瓦纳的Tsepamo研究显示，孕期接受EFV 600mg 方案比以洛匹那韦/利托那韦（LPV/r）或NVP为基础的方案更安全，安全性与DTG孕期结局类似且无相关新生儿神经管缺陷风险[18]
- 药物代谢及药效动力学研究显示， EFV 400mg药物浓度仅轻微下降且维持在药效范围内[6]
- 具有高水平治疗前耐药者，不建议使用EFV 400mg和EFV 600mg方案
- EFV 400mg可联合用于含利福平的抗结核治疗，联合治疗耐受性良好且能维持有效的血浆药物浓度

6. Lamorde M, Wang X, Neary M, Bisdomini E, Nakalema S, Byakika-Kibwika P et al. Pharmacokinetics, pharmacodynamics, and pharmacogenetics of efavirenz 400 mg once daily during pregnancy and post-partum. Clin Infect Dis. 2018;67:785–90.
18. Zash R, Jacobson DL, Diseko M, Mayondi G, Mmalane M, Essex M et al. Comparative safety of antiretroviral treatment regimens in pregnancy. JAMA Pediatr. 2017;171:e172222.

经治二线方案推荐

WHO 2019指南：二线ART方案推荐意见

二线ART方案推荐意见	相比2018年版更新点
1. 推荐DTG联合理想的NRTI骨干药物为以非-DTG为基础的方案失败者的首选二线方案 ✓ 成人及青少年【附条件推荐，中等确定性证据】 ✓ 获批DTG剂量的儿童【附条件推荐，低确定性证据】	• **适用人群扩展**：“成人及青少年”包含孕妇、育龄期女性、合并TB者等全人群
2.推荐增强型蛋白酶抑制剂联合理想的NRTI骨干药物为以DTG为基础的一线方案失败者的首选二线方案【强推荐，中等确定性证据】	/

8. Update of recommendations on first- and second-line antiretroviral regimens. Geneva, Switzerland: World Health Organization; 2019(WHO/CDS/HIV/19.15).Licence: CC BY-NC-SA 3.0 IGO.

人群	一线方案失败	首选二线方案	备选二线方案
成人及青少年[a]	TDF[b] + 3TC (or FTC) + DTG[c]	AZT + 3TC + ATV/r (or LPV/r)	AZT + 3TC + DRV/r[d]
	TDF + 3TC (or FTC) + EFV(or NVP)	AZT + 3TC + DTG[c]	AZT + 3TC + ATV/r (or LPV/r or DRV/r)[d]
	AZT + 3TC + EFV (or NVP)	TDF[b] + 3TC (or FTC) + DTG[c]	TDF[b] + 3TC (or FTC) + ATV/r(or LPV/r or DRV/r)[d]
儿童及新生儿	ABC + 3TC + DTG[e]	AZT+ 3TC + LPV/r (or ATV/r[f])	AZT + 3TC + DRV/r[g]
	ABC (or AZT) + 3TC + LPV/r	AZT (or ABC) + 3TC + DTG[e]	AZT (or ABC) + 3TC + RAL
	ABC (or AZT) + 3TC + EFV	AZT (or ABC) + 3TC + DTG[e]	AZT (or ABC) + 3TC + LPV/r (or ATV/r[f])
	AZT + 3TC + NVP	ABC + 3TC + DTG[e]	ABC + 3TC + LPV/r (or ATV/r[f] or DRV/r[g])

[a]若以PTs为一线方案，即ATV/r（或LPV/r或DRV/r，基于战略性考虑）+TDF+3TC（或FTC），则二线方案为AZT + 3TC + DTG

[b]为育龄期女性提供有效避孕措施。可向希望怀孕或未能获得有效避孕措施且已充分了解新生儿神经管缺陷风险可能增加的育龄期女性开具DTG处方（从怀孕到前三个月结束）。确认怀孕三个月以上者，应在怀孕期间启动或继续使用DTG

[c]TAF在特殊情境下可作为成人及青少年的备选NRTI

[d]RAL + LPV/r可作为成人及青少年的备选二线方案

[e]欧洲药品局目前仅批准DTG用于体重15kg及以上儿童，体重20kg以上儿童可使用成人50mg分散片。更低龄儿童的适用剂量研究仍在进行，有望于2020年早期出结果，目前仍采用WHO 2016年指南推荐（基于PI的方案适用于NNRTIs方案失败的儿童，RAL适用于LPV/r失败的儿童）。TAF可作为体重25kg及以上儿童的备选NRTI

[f]ATV/r可作为LPV/r用于三个月龄以上儿童的备选方案，但需考虑针对6岁以下儿童的合适配方有限、固定剂量配方欠缺以及利托那韦增强剂的分离需求等因素

[g]DRV避免用于三岁以下儿童，且需与合适剂量的利托那韦联用

8. Update of recommendations on first- and second-line antiretroviral regimens. Geneva, Switzerland: World Health Organization; 2019(WHO/CDS/HIV/19.15).Licence: CC BY-NC-SA 3.0 IGO.

WHO推荐DTG为首选二线方案原因

- **DTG联合理想的NRTI骨干药物：**
  - **疗效及安全性**
    - ✓ 较基于蛋白酶抑制剂（PI）的二线方案安全有效
  - **药物间相互作用（DDI）少**
  - **药片负担小**
    - ✓一天一次固定剂量可及性
  - **花费低**

DTG二线治疗疗效及安全性优于LPV/r

Dolutegravir versus ritonavir-boosted lopinavir both with dual nucleoside reverse transcriptase inhibitor therapy in adults with HIV-1 infection in whom first-line therapy has failed (DAWNING): an open-label, non-inferiority, phase 3b trial

Michael Aboud, Richard Kaplan, Johannes Lombaard, Fujie Zhang, José A Hidalgo, Elmira Mamedova, Marcelo H Losso, Ploenchan Chetchotisakd, Carlos Brites, Jörg Sievers, Dannae Brown, Judy Hopking, Mark Underwood, Maria Claudia Nascimento, Yogesh Punekar, Martin Gartland, Kimberly Smith

Summary

Background Doubts exist regarding optimal second-line treatment options for HIV-1-infected patients in resource-limited settings. We assessed safety and efficacy of dolutegravir compared with ritonavir-boosted lopinavir, plus two nucleoside reverse transcriptase inhibitors (NRTIs) in adults in whom previous first-line antiretroviral therapy with a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two NRTIs has failed.

Lancet Infect Dis 2019

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DTG二线治疗疗效及安全性优于LPV/r

主要研究终点	研究数量	结论	效果		证据质量
			相对 (95% CI)	绝对 (95% CI)	
不良反应事件	1	DTG 更好	0.63 (0.45 至 0.89)	每1000例少103 例 (从少187 例到少25 例)	高
病毒抑制(48周)	1	DTG 更好	2.11 (1.45至3.21)	每1000例多109 例 (从多54 例到多154例)	中
治疗中断(总体)	1	DTG 更好	0.76 (0.44至1.3)	每1000例少26 例 (从少45 例到少2 例)	中
治疗相关的不良反应事件	1	DTG 更好	0.31 (0.21至0.45)	每1000例少47例 (从少66 例到少31 例)	低

9. Steve Kanters, For WHO ARV GDG, 16-18 May 2018. WHO, 2018.

在治转换方案推荐

WHO 2019指南：在治人群转换治疗推荐（1/2）

成人及青少年转换至TDF+3TC+DTG

转换情景	转换方案	备注
临床失败或免疫学失败或病毒载量未抑制者	转换至AZT+3TC+**DTG** or PI/r[c]	• DTG与非活跃NRTI骨干药物联用的疗效证据尚缺 • 提供依从性支持
病毒载量抑制者	或可依据国家指南替代为TDF+3TC+**DTG**	• 药物供给与患者选择中应考虑替代治疗 • 替代治疗可能产生新的副作用及依从性干预 • DTG方案更具持久性和长期性
临床或免疫学稳定[d]但病毒载量未知者	替代为基于DTG的方案前，优先进行病毒载量检测，或考虑其他项目/临床指标	• DTG与非活跃NRTI骨干药物联用的疗效证据尚缺 • 提供依从性支持
不理想的一线ART方案治疗稳定者[d]	替代为TDF+3TC+**DTG**	• 替代治疗可能产生新的副作用 • 提供依从性支持

[a]为育龄期女性提供有效避孕措施。可向希望怀孕或未能获得有效避孕措施且已充分了解新生儿神经管缺陷风险可能增加的育龄期女性开具DTG处方（从怀孕到前三个月结束）。

[b]确认怀孕三个月以上者，应在怀孕期间启动或继续使用DTG

[c]在依从性评估和持续的病毒载量监测以后

[d]定义为基于国家指南的稳定

8. Update of recommendations on first- and second-line antiretroviral regimens. Geneva, Switzerland: World Health Organization; 2019(WHO/CDS/HIV/19.15).Licence: CC BY-NC-SA 3.0 IGO.

WHO 2019指南：在治人群转换治疗推荐（2/2）

儿童转换至理想的ART方案

在治方案	体重	理想转换方案	考虑
AZT+3TC+NVP AZT+3TC+EFV ABC+3TC+NVP	<20 kg	ABC+3TC+LPV/r	• 若状况稳定，儿童体重达到20kg时可转换至DTG
	20-30 kg	ABC+3TC+**DTG**	• 若状况稳定，儿童体重达到30kg时可转换至TDF+3TC+DTG
	>30 kg	TDF+3TC+**DTG**	\
ABC+3TC+EFV	<20 kg	除非治疗失败，体重达到20kg前避免转换	• 一旦体重达到20kg，转换至DTG每日一次有获益价值
	20-30 kg	ABC+3TC+**DTG**	• 若状况稳定，儿童体重达到30kg时可转换至TDF+3TC+DTG
	>30 kg	TDF+3TC+**DTG**	\
ABC+3TC+LPV/r AZT+3TC+LPV/r	<20 kg	除非治疗失败，体重达到20kg前避免转换	• 保证用药的同时尽可能减少药片负担 • AZT+3TC+LPV/r转换为ABC+3TC+LPV/r可减少药片负担，同时保持NRTI的抗病毒优势
	20-30 kg	ABC+3TC+**DTG**	• 若状况稳定，儿童体重达到30kg时可转换至TDF+3TC+DTG
	>30 kg	TDF+3TC+**DTG**	\

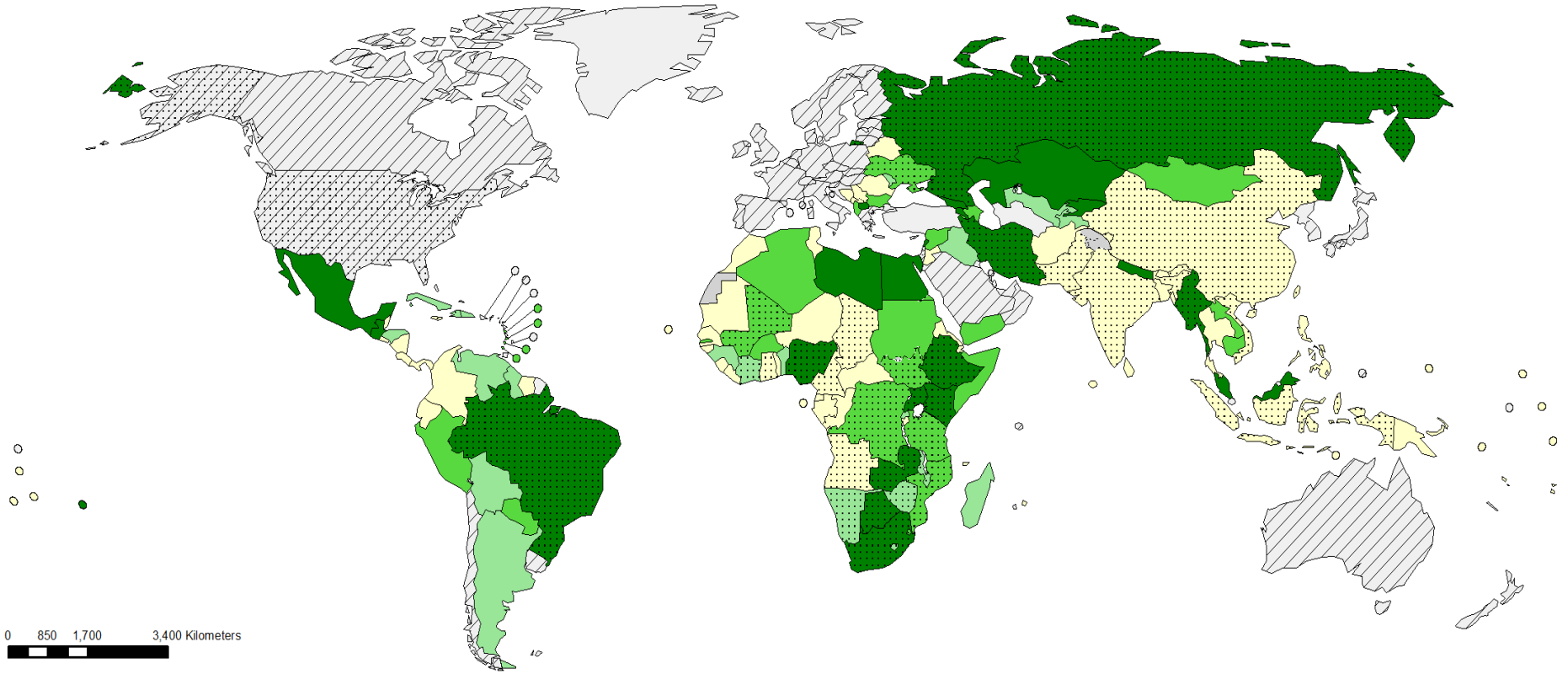
8. Update of recommendations on first- and second-line antiretroviral regimens. Geneva, Switzerland: World Health Organization; 2019(WHO/CDS/HIV/19.15).Licence: CC BY-NC-SA 3.0 IGO.

WHO 2019推荐DTG转换治疗原因

- **基于DTG优势**
  - ✓ 疗效
  - ✓ 安全性
  - ✓ 药物间相互作用
  - ✓ 基因性耐药屏障
  - ✓ ……

- **基于DTG使用的国际现状**
  - ✓ 目前，中低收入国家有>1,000,000HIV感染者使用DTG
  - ✓ 博茨瓦纳、巴西、肯尼亚、尼日利亚和乌干达已采纳DTG作为首选一线用药
  - ✓ 截至2019年早期，已有超过75个中低收入国家将DTG纳入国家指南，超过35个中低收入国家开始采购期待第一批DTG配方药

DTG使用的国际现状——
98 (51%) 个中低收入国家将DTG纳入国家指南（2017-2018）



Global AIDS Monitoring (UNAIDS/WHO/UNICEF) and WHO HIV Country Intelligence Tool, 2018

Reference：https://programme.aids2018.org/PAGMaterial/PPT/6583_4160/First_Second_PEP_ARV%20guidelines_Doherty_24%20July%202018_SHORT_2.pptx

DTG转换治疗的临床与实施考虑

- DTG避免与抗痉挛药（如苯妥英钠、苯巴比妥）、含阳离子制酸剂（如钙、镁）、泻药、多种维生素补剂合用

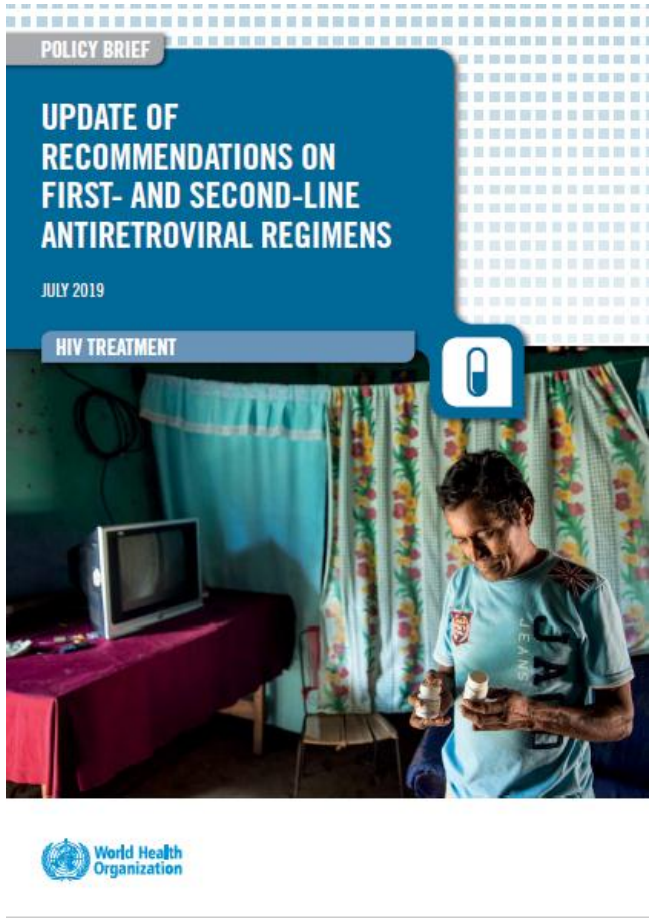
- 风险整合可能导致DTG剂量治疗未达水平，故当联合用药不可避免时，DTG应在含多价阳离子药物使用前2小时或使用后6小时服用[19]

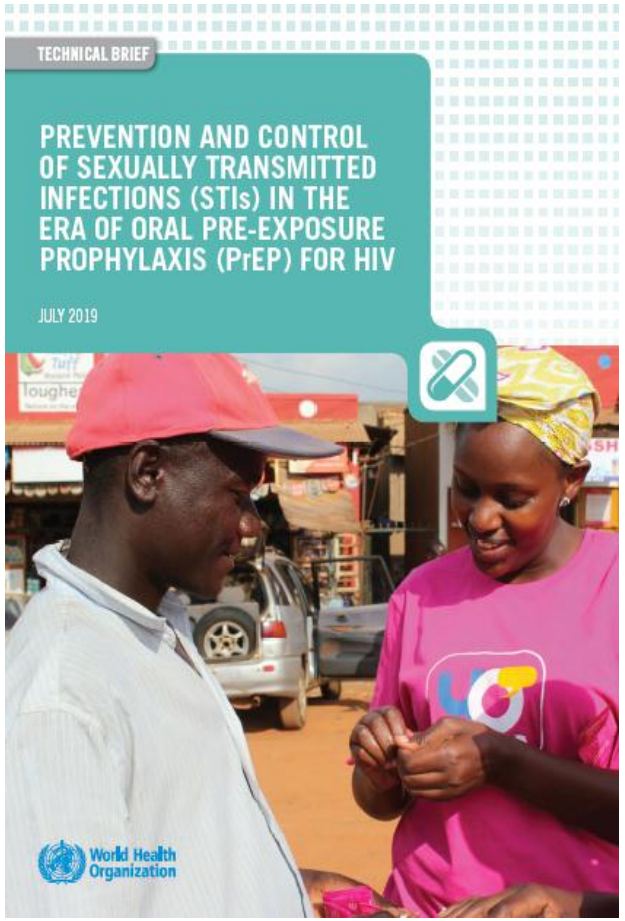
- WHO指南推荐进行病毒载量常规常规监测与必要时检测：虽然病毒载量检测并非转换治疗时必需，但转换方案前未检测过病毒载量者需在转换后优先进行病毒载量检测，进行ARV药物转换时未实施病毒载量检测的国家，也应密切监测人群病毒载量水平和耐药情况

19. HIV drug interactions [online database]. Liverpool: University of Liverpool; 2018 (https://www.hiv-druginteractions.org, accessed 10 July 2019).

暴露前/后预防推荐

WHO 暴露前/后预防(PrEP/PEP) 推荐

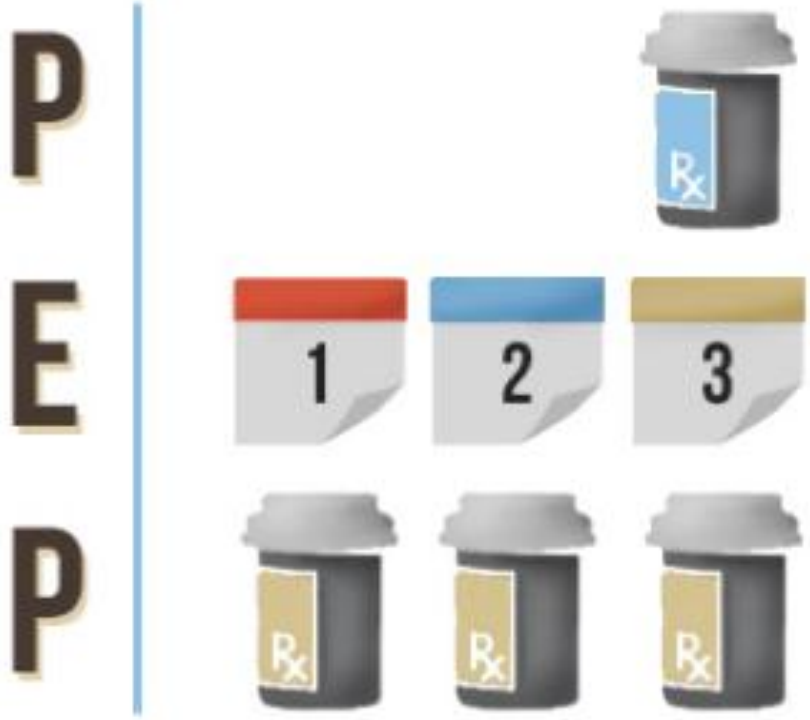




WHO指出并强调了高危人群采取暴露前/后预防的必要性

1 Update of recommendations on first- and second-line antiretroviral regimens. Geneva, Switzerland: World Health Organization; 2019(WHO/CDS/HIV/19.15).Licence: CC BY-NC-SA 3.0 IGO..
2. PREVENTION AND CONTROL OF SEXUALLY TRANSMITTED INFECTIONS (STIS) IN THE ERA OF ORAL PRE-EXPOSURE PROPHYLAXIS (PREP) FOR HIV 2019(WHO/CDS/HIV/19.9).

暴露后预防（PEP）



PEP involves taking anti-HIV drugs as soon as possible after having been exposed.

To be effective, PEP must begin within 72 hours of exposure, before the virus has time to rapidly replicate in your body.

PEP consists of 2-3 antiretroviral medications taken for 28 days.

暴露后预防(PEP)是指在暴露于HIV病毒后尽快的服用抗HIV的药物，以降低HIV感染的风险。

WHO：PEP 选择药物考虑因素

4.3. Implementation considerations

The uptake and completion rates for HIV PEP are suboptimal, and the recommendations for HIV PEP regimens should be considered together with existing WHO recommendations aimed at improving completion rates for HIV PEP, including adherence support and providing a full 28-day course of medication at the first clinic visit *(2,91)*.

Choice of HIV PEP regimen should consider the ARV drugs already being procured within national HIV programmes. Additional considerations include the availability of heat-stable formulations, daily dosing, availability and affordability (Table 3).

People may be subject to ongoing high risk of exposure to HIV, leading to multiple prescriptions for PEP. In such situations, health providers should discuss with their clients the potential benefits of transitioning to HIV pre-exposure prophylaxis (PrEP) *(96,97)*.

Table 3. Characteristics of third drug options for post-exposure prophylaxis

Choice criteria	ATV/r	DRV/r	DTG	LPV/r	RAL
Discontinuation rate in HIV post-exposure prophylaxis	9.3%	0.9%	1.4%	5.2%	2.7%
Dosing schedule	Once daily	Once daily	Once daily	Twice daily	Once or twice daily
Availability as a heat-stable formulation	No	No	Yes	Yes	Yes
Accessibility in countries (registration status)	Low	Low	Moderate	High	Low
Acceptability to health providers	High	High	High	High	High
Affordability	Moderate	Moderate	High	Moderate	Low
Age indication	>3 months	>3 years	>6 years	>14 days	Birth

PEP 药物的选择应考虑药物可及性、热稳定性、药片负担和可负担性

1 Update of recommendations on first- and second-line antiretroviral regimens. Geneva, Switzerland: World Health Organization; 2018.

WHO：PEP 方案推荐

Recommendations

Overall

An HIV post-exposure prophylaxis regimen with two ARV drugs is effective, but three drugs are preferred *(conditional recommendation, low-certainty evidence)*[a]

Adults and adolescents

TDF + 3TC (or FTC) is recommended as the preferred backbone regimen for HIV post-exposure prophylaxis *(strong recommendation, low-certainty evidence)*[a]

NEW DTG is recommended as the preferred third drug for HIV post-exposure prophylaxis *(strong recommendation, low-certainty evidence)*[b]

NEW When available, ATV/r, DRV/r, LPV/r and RAL may be considered as alternative third drug options for post-exposure prophylaxis *(conditional recommendation, low-certainty evidence)*

Children[c]

AZT + 3TC is recommended as the preferred backbone regimen for HIV post-exposure prophylaxis for children. ABC + 3TC or TDF + 3TC (or FTC) can be considered as alternative regimens *(strong recommendation, low-certainty evidence)*[a]

NEW DTG is recommended as the preferred third drug for HIV post-exposure prophylaxis for children for whom an approved DTG dosing is available *(strong recommendation, low-certainty evidence)*

NEW When available, ATV/r, DRV/r, LPV/r and RAL may be considered as alternative third drug options for post-exposure prophylaxis *(conditional recommendation, low-certainty evidence)*

[a] WHO 2016 consolidated guidelines on the use of ARV drugs for treating and preventing HIV infection.
[b] See Box 1 on women and adolescent girls of childbearing potential using DTG.
[c] The choice of ARV drugs for children will depend on the availability of approved dosing and age-appropriate formulations for children. Use of DTG applies to all infants and children for whom an approved DTG dosing is available.

成人及青少年：
- TDF+3TC（或FTC）是PEP的首选推荐的骨干药物；
- DTG被推荐为首选的第三类药物；
- ATV/r, DRV/r, LPV/r以及RAL可作为备选的第三类药物；

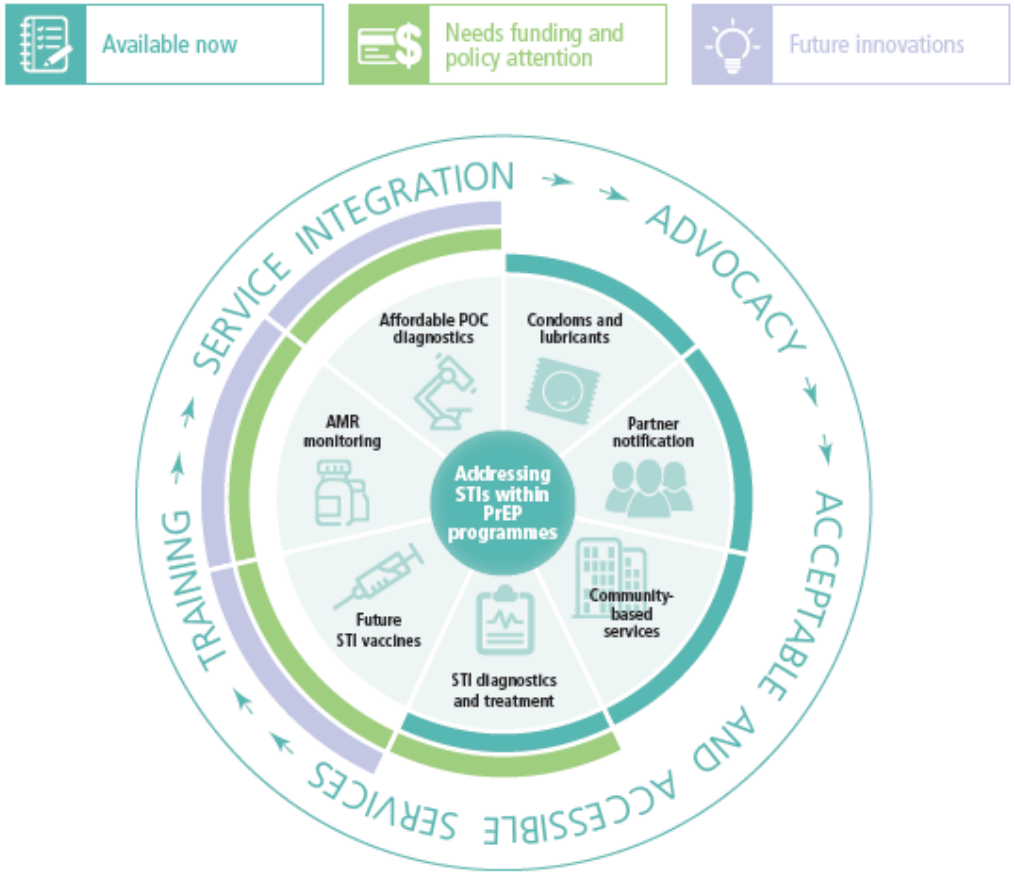
儿童：
- ≤10岁儿童：AZT+3TC是PEP的首选推荐的骨干药物；ABC+3TC或者TDF+3TC（或FTC）可作为备选方案；
- DTG被推荐为首选的第三类药物；
- ATV/r, DRV/r, LPV/r以及RAL可作为备选的第三种药物；

1 Update of recommendations on first- and second-line antiretroviral regimens. Geneva, Switzerland: World Health Organization; 2018.

WHO：PrEP 推荐

PrEP现有和未来干预措施

Figure 1. Existing and future interventions for improving STI prevention and control by leveraging PrEP scale-up



WHO 推荐TDF/FTC(3TC)用作PrEP使用药物

WHO recommends offering oral pre-exposure prophylaxis (PrEP) to people at substantial risk of HIV as part of comprehensive HIV prevention *(1)*. PrEP is the use of oral tenofovir disoproxil fumarate (TDF) or co-formulated TDF/emtricitabine (TDF/FTC) or co-formulated TDF/lamivudine (TDF/3TC) by HIV-negative people to prevent HIV acquisition. PrEP has been shown to be effective in a wide range of HIV-negative populations. WHO considers FTC and 3TC interchangeable, both for treatment and for prevention of HIV infection *(2–4)*.

An increasing number of countries are adopting policies endorsing PrEP for HIV prevention. A global review found that 40 countries had incorporated oral PrEP into their policies or guidelines by the end of 2018 *(5)*. The use of PrEP has grown substantially over time, particularly among men who have sex with men in high-income settings, where PrEP was introduced early on, as well as among other priority populations in low- and middle-income settings.

Emerging evidence from clinical research that different dosing strategies can be effective provides an opportunity to offer flexibility, choice and convenience to individuals who can benefit from PrEP and is considered by WHO in updating its guidance to countries. WHO also promotes the use of differentiated approaches for reaching men who have sex with men and other key populations[1] across the HIV services continuum, including for PrEP *(6)*. These new strategies have the potential to reduce the cost of drugs, to reduce pill burden and toxicity and to improve continuation among those who find daily pill-taking challenging.

Evidence that different dosing strategies can be effective offers users of PrEP flexibility, choice and convenience.

In 2016 WHO published the *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed*. This publication described the high efficacy of PrEP dosing both before and after sex among men who have sex with men who reported frequent sexual activity in the IPERGAY trial – a regimen now called event-driven PrEP (ED-PrEP) *(1)*. In those guidelines WHO noted that how best to adapt the PrEP recommendations to diverse and changing sexual practices would be an important focus for further implementation research.

.1. PREVENTION AND CONTROL OF SEXUALLY TRANSMITTED INFECTIONS (STIS) IN THE ERA OF ORAL PRE-EXPOSURE PROPHYLAXIS (PREP) FOR HIV 2019(WHO/CDS/HIV/19.9).

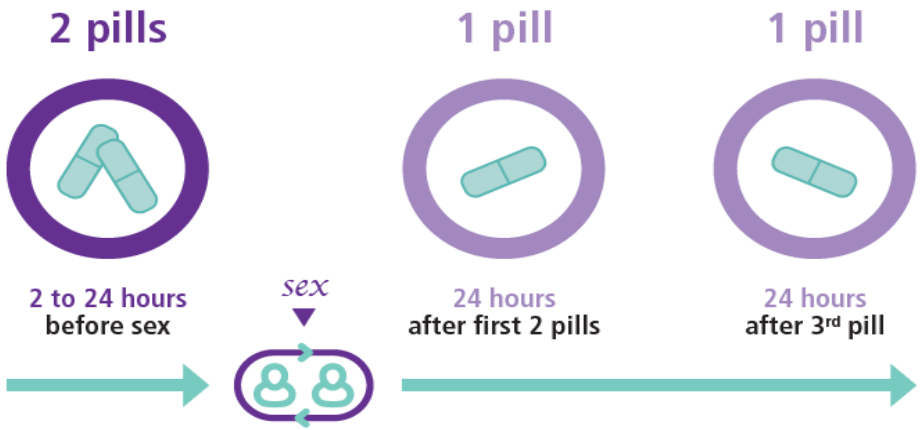
WHO：ED-PrEP in MSM

- ED-PrEP在降低通过接受性和/或插入男男同性性行为感染艾滋病毒风险方面是安全且高效的。它可以作为MSM 每日剂量PrEP的替代。来自现有的试验和最近在阿姆斯特丹完成的为期两年的实证研究表明，ED-PrEP在预防MSM艾滋病毒感染方面，与每日剂量PrEP一样有效

Table 1. HIV incidence reported from interim analysis of Prevenir study, 2019

PrEP dosing regimen	Follow-up (person-years)	HIV incidence per 100 person-years (95% CI)
TDF/FTC (daily)	1073	0 (0–0.3)
TDF/FTC (ED-PrEP)	1133	0.18 (0.02-0.6)

Source: Molina et al., 2019(47).



For whom is ED-PrEP appropriate?

- a man who has sex with another man:
  - who would find ED-PrEP more effective and convenient
  - who has infrequent sex (for example, sex less than 2 times per week on average)
  - who is able to plan for sex at least 2 hours in advance, or who can delay sex for at least 2 hours

For whom is ED-PrEP NOT appropriate?

- cisgender women or transgender women
- transgender men having vaginal/frontal sex
- men having vaginal or anal sex with women
- people with chronic hepatitis B infection.

ED-PrEP：event driven -PrEP

1.WHAT' S THE 2+1+1? EVENT-DRIVEN ORAL PRE-EXPOSURE PROPHYLAXIS TO PREVENT HIV FOR MEN WHO HAVE SEX WITH MEN. HIV 2019(WHO/CDS/HIV/19.8).

总结

一线ART方案推荐

- **DTG：一线首选，全人群适用**
- EFV 400mg：一线备选
- RAL：新生儿适用

二线ART方案推荐

- DTG：二线首选，全人群适用
- 增强型蛋白酶抑制剂：含DTG一线方案失败后首选

转换治疗方案推荐

- 考虑疗效、安全性、药物间相互作用、耐药屏障……
- 国际形势：中低收入国家尤其是存在NNRTI治疗前耐药的国家，对DTG需求增长

暴露前/后预防

- 在选择药物方案的时候应优先选择毒副作用少，安全，服用简单方便的方案
- 必需要强调联合行为方式的改变来预防感染

THANKS !