TB/HIV co-infection - epidemiological data for the WHO European Region - clinical managment of HIV/TB co-infections

World Health Organization
REGIONAL OFFICE FOR Europe

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Tuberculosis, HIV, Viral Hepatitis and other infections programme

HIV Epidemic trends in the WHO European Region, 2019

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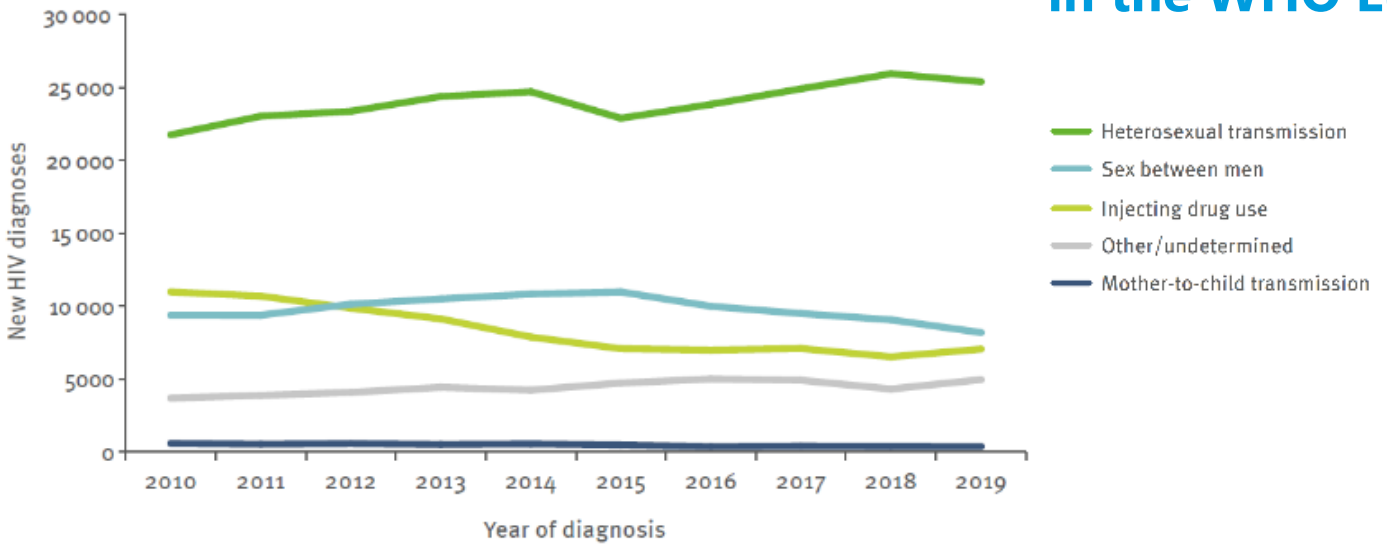
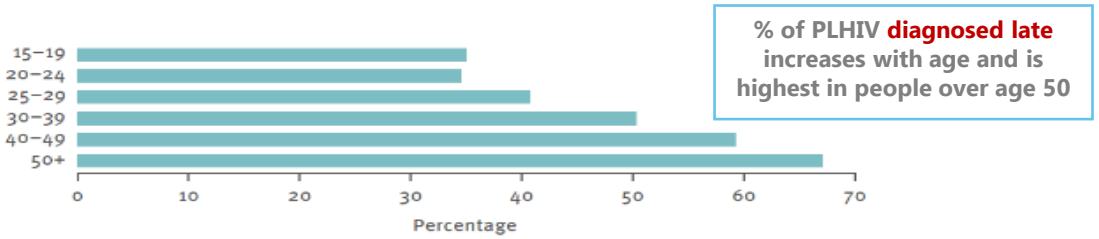
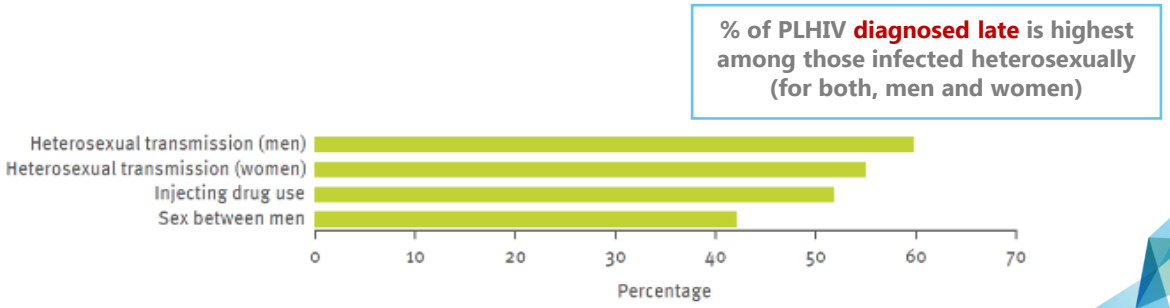
New HIV diagnoses, by transmission mode
WHO European Region, 2010–2019



Late HIV diagnosis remains a challenge
with variation across transmission mode & age





Source: ECDC/WHO (2020). HIV/AIDS Surveillance in Europe 2020– 2019 data

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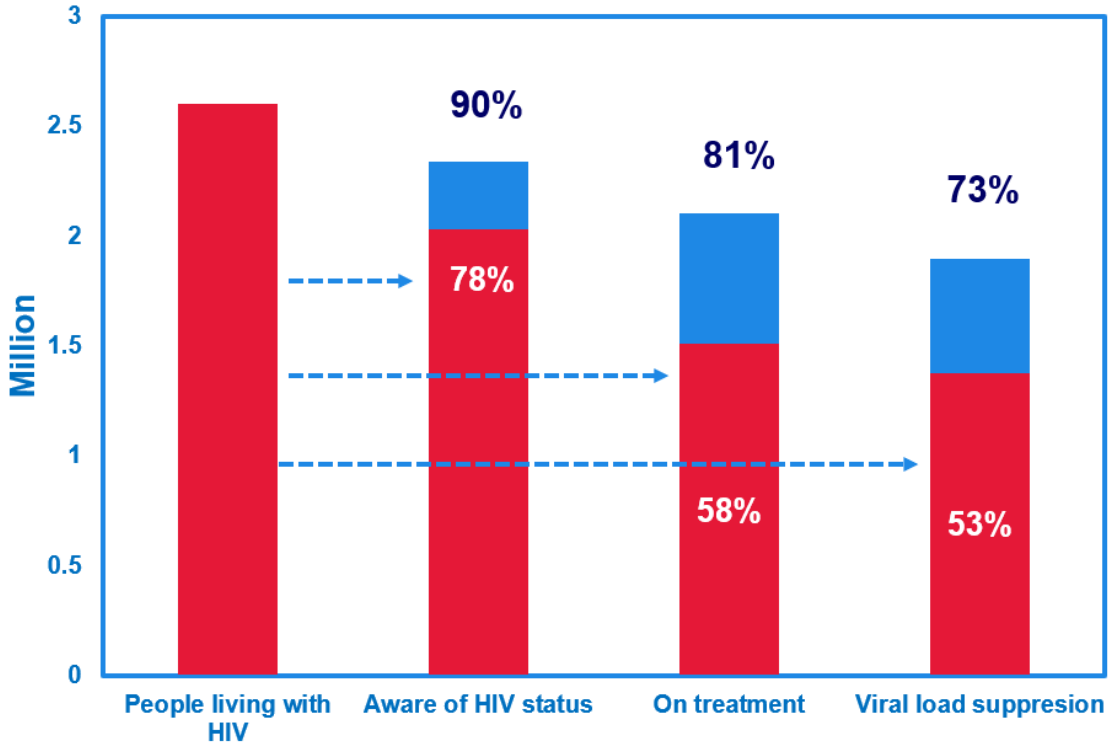
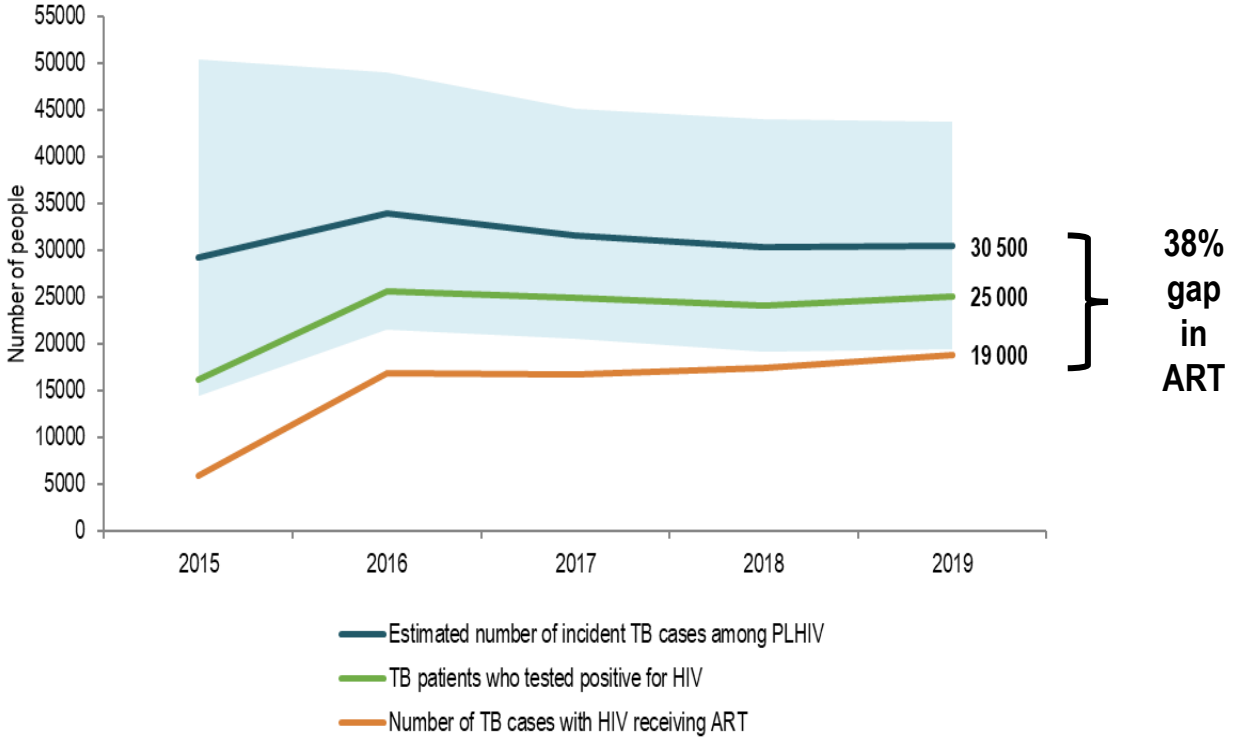
HIV testing and treatment cascade WHO European Region, 2019



Source: UNAIDS/WHO estimates 2019

TB/HIV co-infection diagnosis and treatment cascade
WHO European Region



*In 2019 **82%** of estimated new TB/HIV patients in the WHO European region knew their HIV status*
***76%** of reported HIV-positive TB patients in 2019 were started on antiretroviral therapy*

TB treatment outcomes and TPT among PLHIV
WHO European Region, 2019

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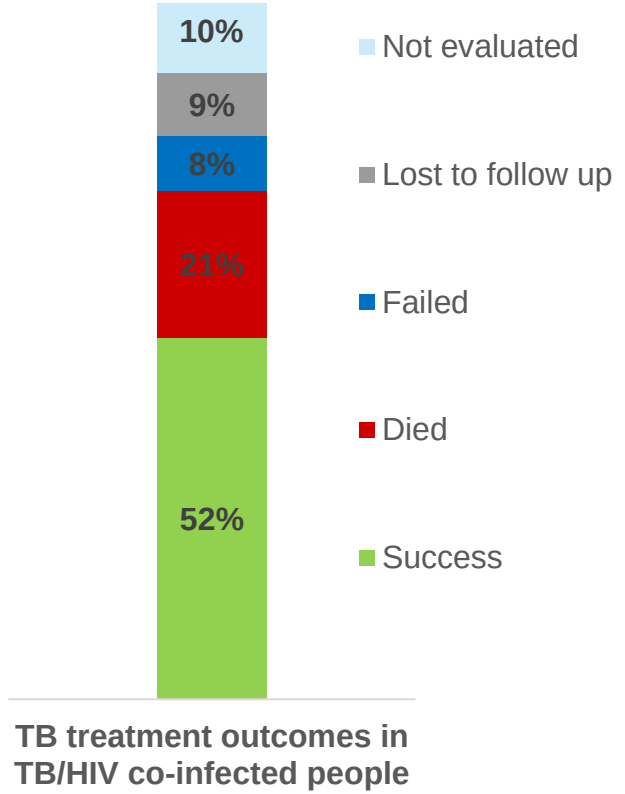
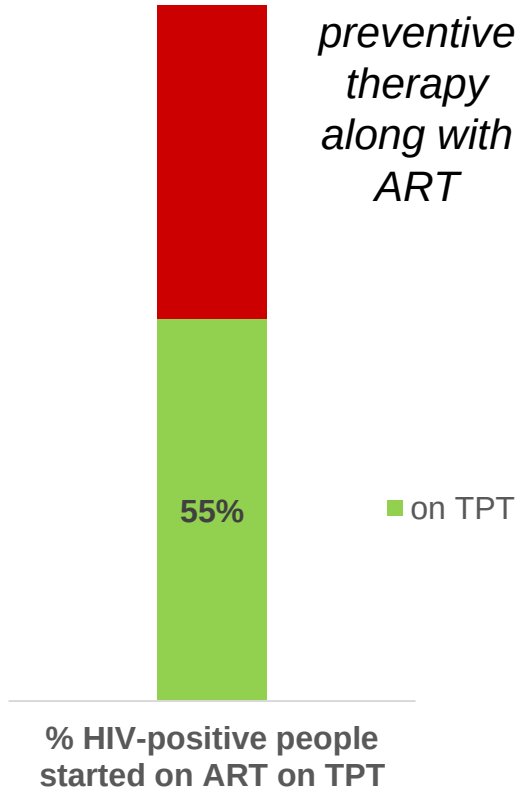
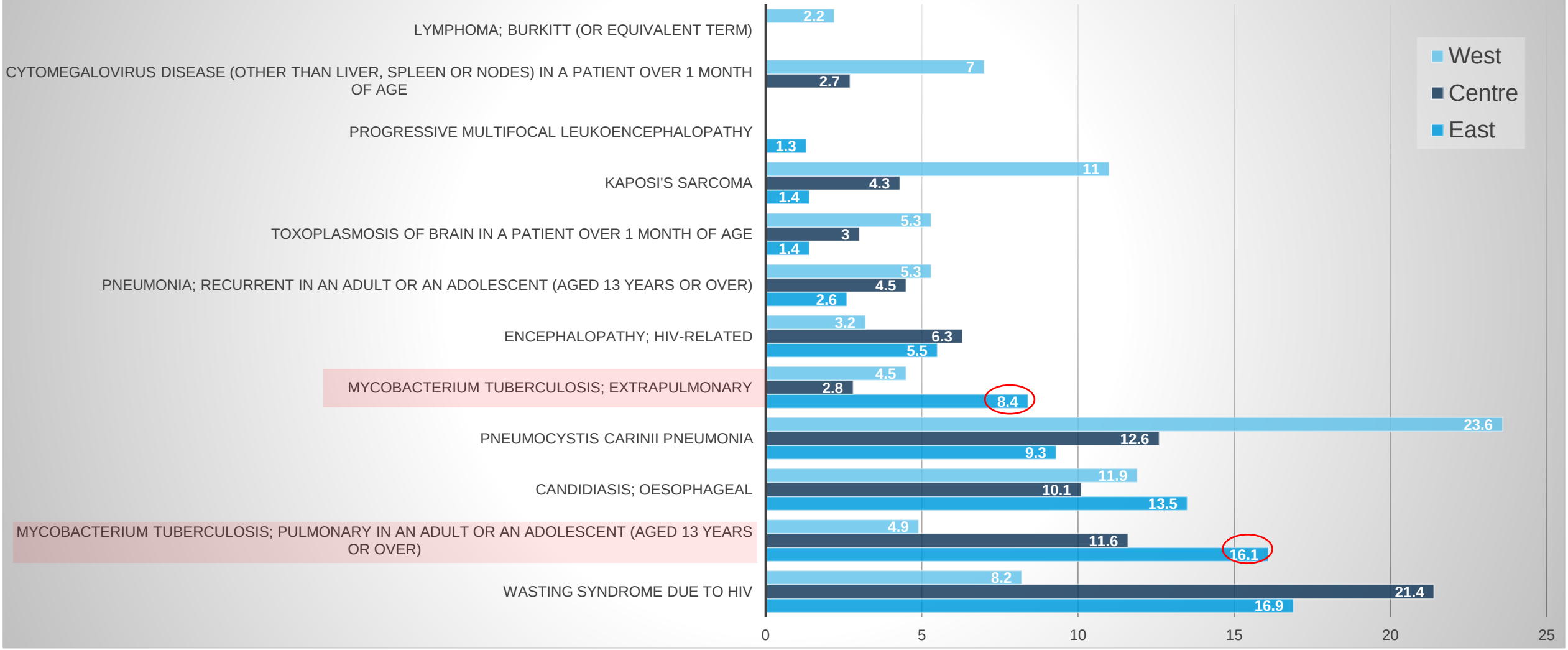


*In 2019, **55%** of PLHIV started TB preventive therapy along with ART*



*In 2019 **52%** of HIV+ TB cases had successful TB treatment outcome, lower than global rate of **76%***

Most common AIDS-indicative diseases diagnosed in 2019, WHO European Region, %

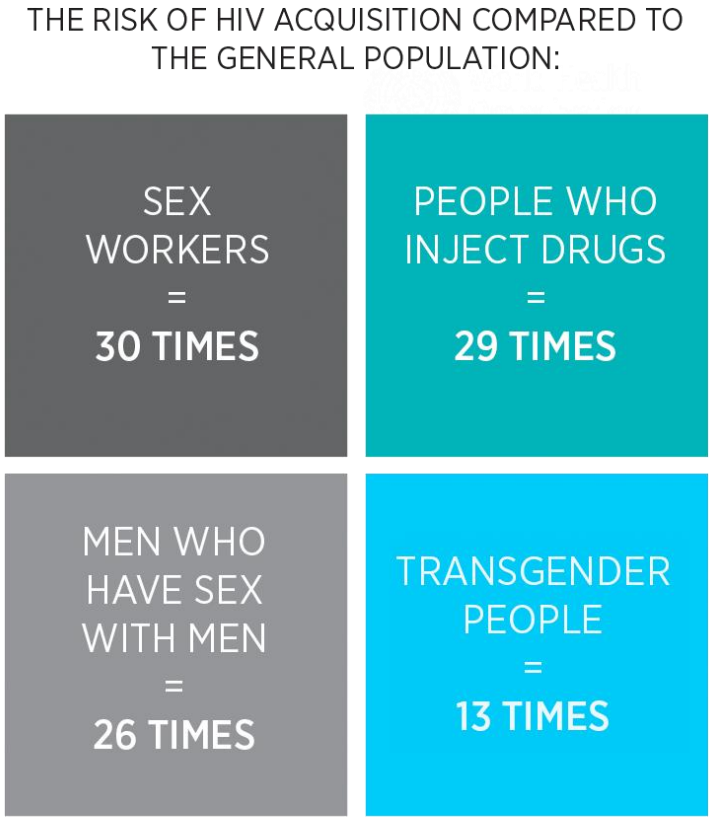


Source: ECDC/WHO (2020). HIV/AIDS Surveillance in Europe 2020– 2019 data

Tuberculosis (TB) in people living with HIV (PLWH)

- **Among** the estimated 38 million **PLHIV**, the **risk of developing active TB is 19 times higher (range 15-22) than among people without HIV**.
- TB is the leading cause of hospital admission and mortality among PLWH.
- **Among people with latent TB infection** (LTBI), HIV-co-infection is the **highest risk** factor **for disease progression**.
- **TB preventive therapy** is **effective**, including **in PLWH**.

Key populations have poor access to HIV and TB services

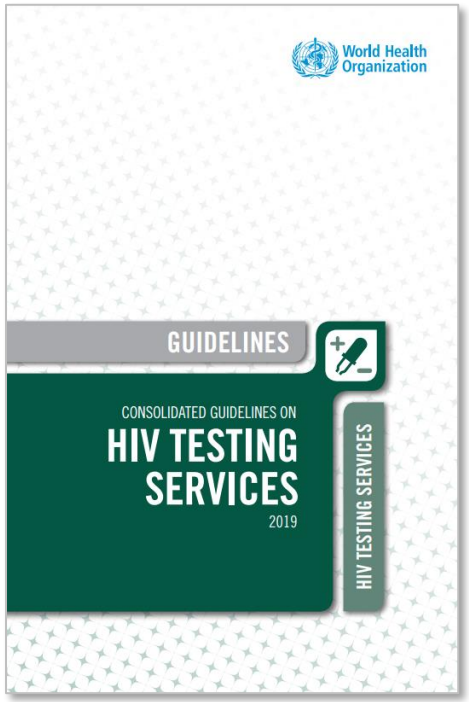


SOURCE: UNAIDS GLOBAL AIDS UPDATE 2020

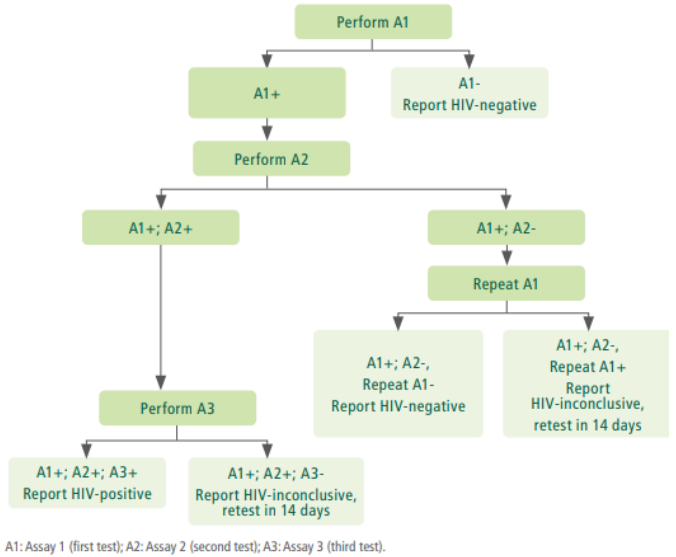
UNAIDS. Global AIDS Update 2020. WHO. Global Tuberculosis Report. 2019.
WHO. Latent tuberculosis infection. Updated and consolidated guidelines for programmatic management. 2018.

HIV Testing Guidance (Dec 2019)

1. **Demand creation:** NEW **Good practice statement** highlighting evidence-based approaches and considerations for the use of incentives for HIV testing services, including linkage.
2. **Counselling message:** ✓ **Updated** messages and guidance on concise communications with emphasis on linkage and latest information on the benefits of treatment and prevention services. (no individual pre-test counselling)
3. **HIV self-testing:** ✓ **Updated** HIV self-testing should be offered as an approach to HIV testing services *(strong recommendation, moderate-quality evidence)*.
4. **Social network-based approaches:** NEW Social network-based approaches can be offered as an HIV testing approach for key populations as part of a comprehensive package of care and prevention *(conditional recommendation, very low-quality evidence)*.
5. **HIV testing strategies:** ✓ **Updated.** In response to changes in the HIV epidemic, WHO encourages countries to move toward using three consecutive reactive tests to provide an HIV-positive diagnosis.
6. **Western blotting:** NEW Western blotting and line immunoassays should not be used in national HIV testing strategies and algorithms *(strong recommendation, low-quality evidence)*.



Given latest diagnostic technologies HIV diagnosis can be confirmed faste and should not take longer than 14 days



A1: Assay 1 (first test); A2: Assay 2 (second test); A3: Assay 3 (third test).

https://www.who.int/publications/i/item/978-92-4-155058-1

Intervention	Individual benefit	Community benefit
Antiretroviral therapy	Decreased risk of *Mycobacterium tuberculosis* infection and active TB; decreased risk of XDR-TB and MDR-TB	Prevention of HIV transmission to partners and children; decreased incidence and prevalence of HIV infection; decreased incidence and prevalence of TB, including XDR-TB and MDR-TB
Intensified case finding for TB	Earlier TB diagnosis and treatment; reduced morbidity and mortality; earlier use of isoniazid preventative therapy for persons found not to have TB	Diminished transmission of *M. tuberculosis* to health care workers, clients, partners, families, and the community; decreased incidence and prevalence of TB, including XDR-TB and MDR TB
Infection control for TB	Decreased risk of infection with *M. tuberculosis* and development of active TB; decreased risk of reinfection with *M. tuberculosis,* including XDR-TB and MDR-TB	Diminished transmission of *M. tuberculosis* to health care workers, clients, partners, families, and communities; decreased incidence and prevalence of TB, including XDR-TB and MDR-TB
Isoniazid preventative treatment	Reduction in the risk of active TB; prevention of *M. tuberculosis* infection	Decreased incidence and prevalence of TB; decreased transmission of *M. tuberculosis,* including XDR-TB and MDR-TB
Combined HIV prevention[a]	Decreased risk of HIV infection; earlier diagnosis and treatment of HIV infection; decreased HIV/AIDS-related illnesses; decreased risk of *M. tuberculosis* infection and active TB; decreased risk of XDR-TB and MDR-TB	Diminished incidence, prevalence, and transmission of HIV infection; diminished transmission of *M. tuberculosis* infection, diminished incidence and prevalence of TB; decreased incidence and prevalence of XDR-TB and MDR-TB

NOTE. ART, antiretroviral therapy; MDR, multidrug-resistant; XDR, extensively drug-resistant.

[a] Partial list includes behavior modification; couples counseling and testing for HIV with improved access to testing for clients to TB services, partners, and family members; early access to ART, including for patients with TB, partners, and family members with HIV infection; and structural interventions (eg, socioeconomic and legal).

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Interventions to Prevent Tuberculosis (TB) in People Living with HIV

- **Antiretroviral treatment**
- **The WHO three "I"s strategy:**
  1. Intensified case finding (ICF)
  2. Isoniazid preventive therapy (IPT)
  3. Infection control for tuberculosis (IC)

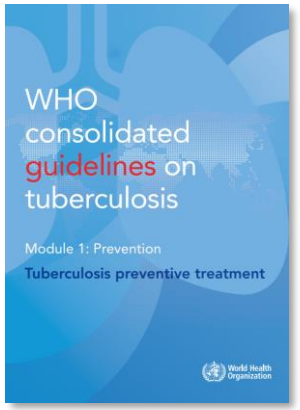
  https://www.who.int/hiv/topics/tb/3is/en/
- **Combination HIV prevention**

Granich R. et al. Preventing TB in People Living with HIV • CID 2010:50 (Suppl 3)
doi: 10.1086/651494 https://pubmed.ncbi.nlm.nih.gov/20397951/

LTBI Treatment in people living with HIV
WHO Recommendations

Adults and adolescents living with HIV, with unknown or a positive tuberculin skin test (TST) and are unlikely to have active TB ***should receive preventive treatment:***

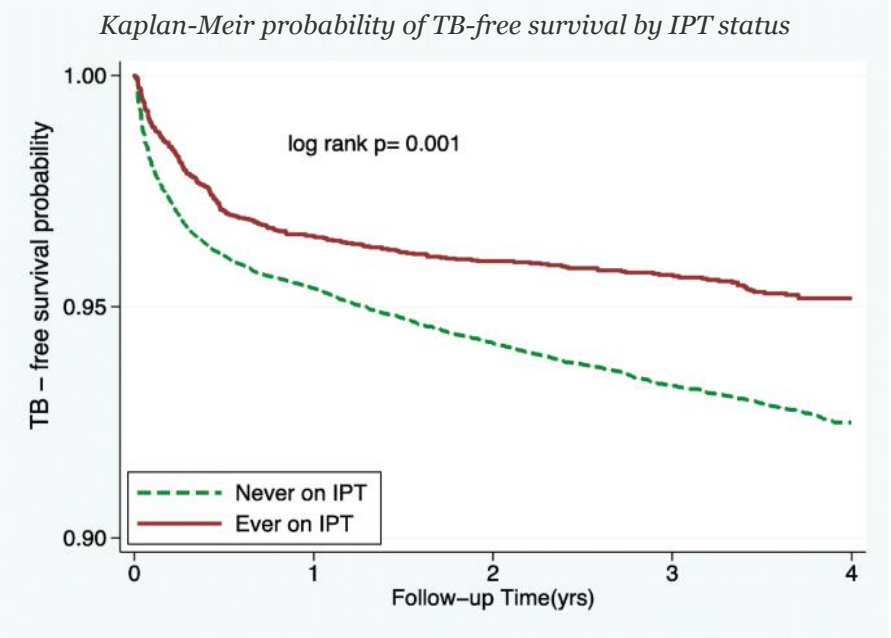
monotherapy with isoniazid for at least 6 months (isoniazid preventive therapy, IPT) OR **treatment with regimens containing a rifamycin (rifampicin or rifapentine).**



- 6 or 9 months of daily isoniazid (**isoniazid preventive therapy (IPT**) *(in PLHIV reduces risk of progressing to TB by 33%)*
- 3 months of weekly rifapentine plus isoniazid
- 3-months of daily isoniazid plus rifampicin
- May also be offered as <u>alternatives</u>:
  - 1-month regimen of daily rifapentine plus isoniazid
  - 4 months of daily rifampicin alone
- 36 months daily IPT in settings with high TB transmission for PLHIV regardless of ART & immunosuppression

https://apps.who.int/iris/bitstream/handle/10665/331170/9789240001503-eng.pdf

Probability of being TB free at the end of follow-up period between IPT and Non-IPT patients.



Patients who received IPT had higher probability of being TB free at the end of follow up period compared to those who never received IPT (log rank $P = 0.001$).

Sabasaba, A., Mwambi, H., Somi, G. *et al.* Effect of isoniazid preventive therapy on tuberculosis incidence and associated risk factors among HIV infected adults in Tanzania: a retrospective cohort study. *BMC Infect Dis* **19,** 62 (2019). https://doi.org/10.1186/s12879-019-3696-x

Current and novel TB preventive treatment regimens + evidence of use with antiretroviral regimens (ART)

González Fernández L et al. *Journal of the International AIDS Society* 2020, **23**:e25438
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25438/full | https://doi.org/10.1002/jia2.25438

Table 1. Tuberculosis preventive therapy and antiretroviral therapy co-administration

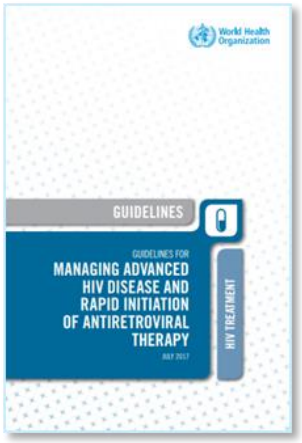
TPT regimen	WHO Recommendation for the TPT regimen	Recommended for children	Compatible ART	Supporting evidence and ongoing DDI trials	Knowledge gaps
IPT	Strong recommendation	Any age	Any		Ideal length of treatment Use in pregnancy
3HR	Strong recommendation	Any age	Any NRTI, possibly including TAF EFV 600 mg QD EFV 400 mg QD with HR DTG 50 mg BID (Adults only) RAL 800 BID	RIFT (TAF + RIF in HV) study [42] STRIDE study [43] Cerrone et al. [37] INSPIRING trial ongoing [44] Taburet et al.[45]	TAF/FTC + RIF in patients with HIV – study in progress in South Africa
3HP	Conditional recommendation	>2 years old only	EFV 600 mg QD DTG 50 mg QD RAL 400 mg BID	Farenc et al. [46] DOLPHIN study [36] Weiner et al. [47]	3HP dosing for children <2 years old 3HP with TAF – healthy volunteer study in progress at US NIH NCT03510468
1HP	Under review	>13 years old only	EFV 600 mg QD	BRIEF-TB PK study [48]	1HP dosing for children <13 years old 1HP with TAF 1HP with dolutegravir – ACTG trial in development (A5372)

1HP, one month daily isoniazid and rifapentine; 3HP, 3 months weekly isoniazid and rifapentine; 3HR, 3 months isoniazid and rifampin; ART, antiretroviral therapy; DDI, drug-drug interaction; DTG, dolutegravir; EFV, efavirenz; HV, healthy volunteer; IPT, isoniazid preventive therapy; NRTI, nucleoside reverse transcriptase inhibitor; PK, pharmacokinetics; RAL, raltegravir; TAF, tenofovir alafenamide; TPT, tuberculosis preventive therapy; WHO, World Health Organization.

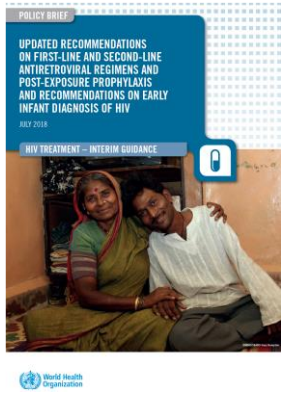
https://onlinelibrary.wiley.com/doi/full/10.1002/jia2.25438

Fast ART initiation (WHO Recommendations)

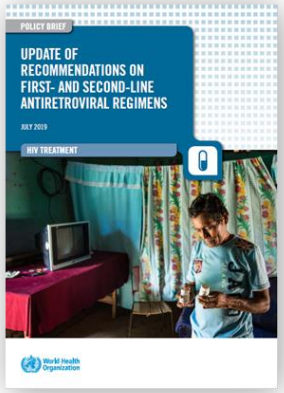
ART should be started once the HIV diagnosis is confirmed in absence of TB and no later than 7 days after the confirmation of HIV diagnosis.
With ref to WHO guidelines 2016-2019



2016
(TLE)



July 2018
(TLD
transition)



July 2019
(TLD for all)

ART initiation in patients with TB/HIV co-infection

- ART should be started in all TB patients living with HIV regardless of their CD4 cell count
  (Strong recommendation, high certainty in the evidence).
- TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment
  (Strong recommendation, high certainty in the evidence).
- HIV-positive patients with CD4 counts less than 50 cells/mm3 should receive ART within the first 2 weeks of initiating TB treatment.

Incoming ART guidelines 2021 may reconsider the time of ART initiation for TB-HIV co-infected patients

ART regimens, WHO guidelines 2019

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Table 1. Preferred and alternative first-line ART regimens

Population	Preferred first-line regimen	Alternative first-line regimen	Special circumstances
Adults and adolescents	TDF + 3TC (or FTC) + DTG[a]	TDF + 3TC + EFV 400 mg[b]	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]
Children	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)
Neonates	AZT + 3TC + RAL[h]	AZT + 3TC + NVP	AZT + 3TC + LPV/r[i]

3TC: lamivudine; ABC: abacavir; AZT: zidovudine; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir/ritonavir; NVP: nevirapine; PI/r: protease inhibitor boosted with ritonavir; RAL: raltegravir; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

[a] Effective contraception should be offered to adult women and adolescent girls of childbearing age or potential. DTG can be prescribed for adult women and adolescent girls of childbearing age or potential who wish to become pregnant or who are not otherwise using or accessing consistent and effective contraception if they have been fully informed of the potential increase in the risk of neural tube defects (at conception and until the end of the first trimester). If women identify pregnancy after the first trimester, DTG should be initiated or continued for the duration of the pregnancy (Box 2).

[b] EFV-based ART should not be used in settings with national estimates of pretreatment resistance to EFV of 10% or higher. DTG-based ART is preferred, and if DTG is unavailable, a boosted PI-based regimen should be used. The choice of PI/r depends on programmatic characteristics.

[c] TAF may be considered for people with established osteoporosis and/or impaired kidney function.

[d] For age and weight groups with approved DTG dosing.

[e] RAL should be used as an alternative regimen only if LPV/r solid formulations are not available.

[f] For age and weight groups with approved TAF dosing.

[g] EFV should not be used for children younger than three years of age.

[h] Neonates starting ART with an RAL-based regimen should transition to an LPV/r solid formulation as soon as possible.

[i] LPV/r syrup or granules can be used if starting after two weeks of age.

Table 2. Preferred and alternative second-line ART regimens

Population	Failing first-line regimen	Preferred second-line regimen	Alternative second-line regimens
Adults and adolescents[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]
Children and infants	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])

3TC: lamivudine; ABC: abacavir; ATV/r: atazanavir/ritonavir; AZT: zidovudine; DRV/r: darunavir/ritonavir; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir/ritonavir; NVP: nevirapine; RAL: raltegravir; TDF: tenofovir disoproxil fumarate.

[a] Sequencing if PIs are used in first-line ART: ATV/r (or LPV/r or DRV/r depending on programmatic considerations) + TDF + 3TC (or FTC) and then AZT + 3TC + DTG in second-line ART.

[b] Effective contraception should be offered to adult women and adolescent girls of childbearing age or potential. DTG can be prescribed for adult women and adolescent girls of childbearing age or potential who wish to become pregnant or who are not otherwise using or accessing consistent and effective contraception if they have been fully informed of the potential increase in the risk of neural tube defects (at conception and until the end of the first trimester). If women identify pregnancy after the first trimester, DTG should be initiated or continued for the duration of the pregnancy (Box 2).

[c] TAF (tenofovir alafenamide) can be used as an alternative NRTI in special situations for adults and adolescents.

[d] RAL + LPV/r can be used as an alternative second-line ART regimen for adults and adolescents.

[e] The European Medicines Agency currently only approves DTG for children weighing at least 15 kg and more widely for children weighing more than 20 kg who can take adult 50-mg film-coated tablets. Studies are ongoing to determine dosing for younger children, with approval expected in early 2020, but the 2016 WHO recommendations for second-line ART still hold (PI-based for children for whom NNRTIs have failed and RAL for children for whom LPV/r has failed). TAF (tenofovir alafenamide) can be used as an alternative NRTI in children weighing at least 25 kg.

[f] ATV/r can be used as an alternative to LPV/r for children older than three months, but the limited availability of suitable formulations for children younger than six years, the lack of a fixed-dose formulation and the need for separate administration of the ritonavir booster should be considered when choosing this regimen.

[g] DRV should not be used for children younger than three years and should be combined with appropriate dosing of ritonavir.

WHO recommends genotyping only in 3rd line ART with treatment optimization purpose.

*Countries should also implement **once in 3 years surveys on PDR and ADR to monitor HIV DR***

3rd line regimens

- DRV/r[a] + **DTG** ± 1-2 NRTIs

a) for PLHIV on ART with experinec of receiving Ips the recommended dose of DRV/r should be 600 mg/100 mg 2 times per day.

Preferred and alternative 1st line and 2nd line ART regimens for TB and HBV co-infections

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Population	First-line ART regimen
HIV and TB coinfection	**TDF/FTC + Dolutegravir** 50 mg BID with rifampicin or switch to rifabutin
	TDF/FTC/Efavirenz 400 mg EFV 400 mg can be co-administered with rifampicin (well tolerated and plasma concentrations maintained above the levels considered to be effective)

Population		Second-line regimen
HIV and TB coinfection	If using rifampicin in TB regimen	**Optimized NRTI backbone plus double-dose DTG (that is, DTG 50 mg twice daily) or double-dose LPV/r (that is, LPV/r 800 mg/200 mg twice daily)[acd]**
	If using rifabutin in TB regimen	**Optimized NRTI backbone plus DTG or boosted PI-containing regimens at standard doses [ac]**
HIV and HBV coinfection	**AZT + TDF + 3TC (or FTC) + (DTG or ATV/r or LPV/r) [bd]**	

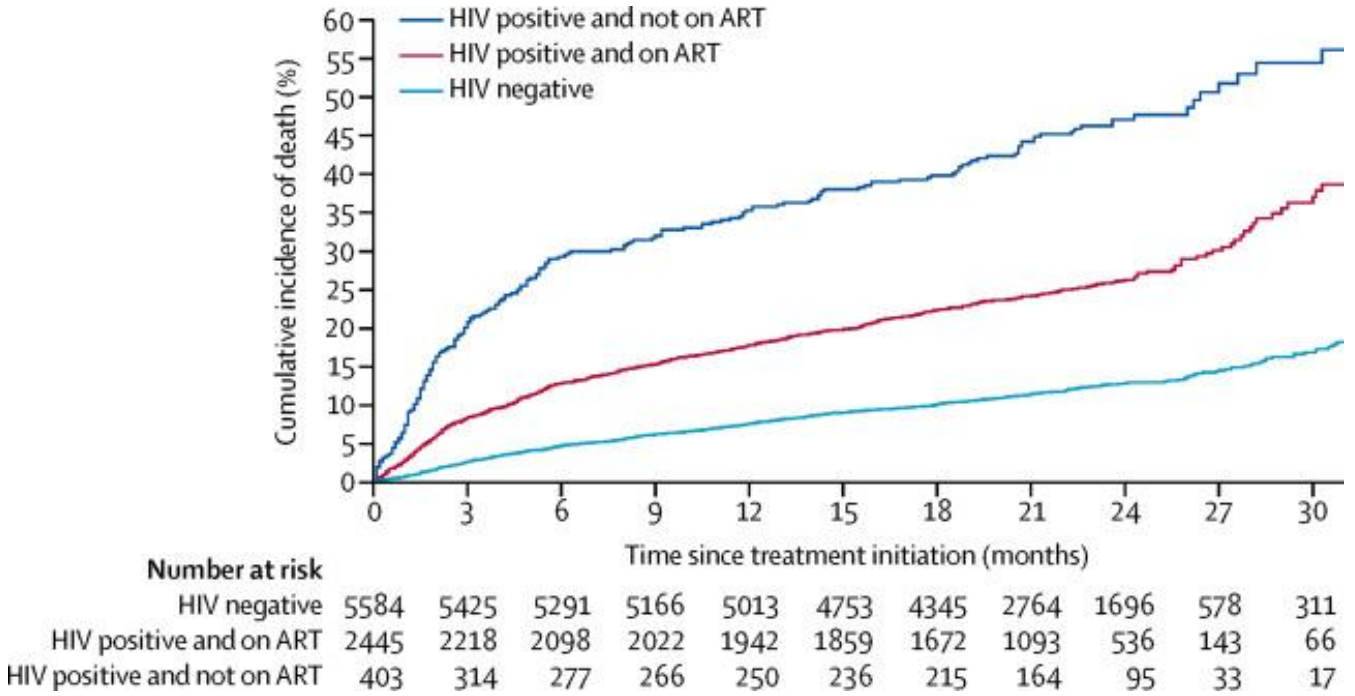
a) If TDF + 3TC (or FTC) was used as the NRTI backbone in the 1st line failing regimen, AZT+3TC should be used in 2nd line and vice-versa.
b) DRV/r can be used as an alternative PI option.
c) In childbearing age women an adolescent girls, DTG can be used if she is on reliable contraception and fully informed and benefit outweighs the risk.
d) Standard LPV dose with an adjusted dose of RTV (that is, LPV400mg/ RTV 400mg twice daily) can be used as alternative options.

Use of ART and effective anti-TB medicines associated with significantly lower death rates

"Among patients with HIV, use of at least one WHO Group A drug and specific use of *moxifloxacin, levofloxacin, bedaquiline*, or *linezolid* were associated with significantly decreased odds of death.

Use of ART and more effective anti-tuberculosis drugs is associated with lower odds of death among HIV-positive patients with multidrug-resistant tuberculosis.

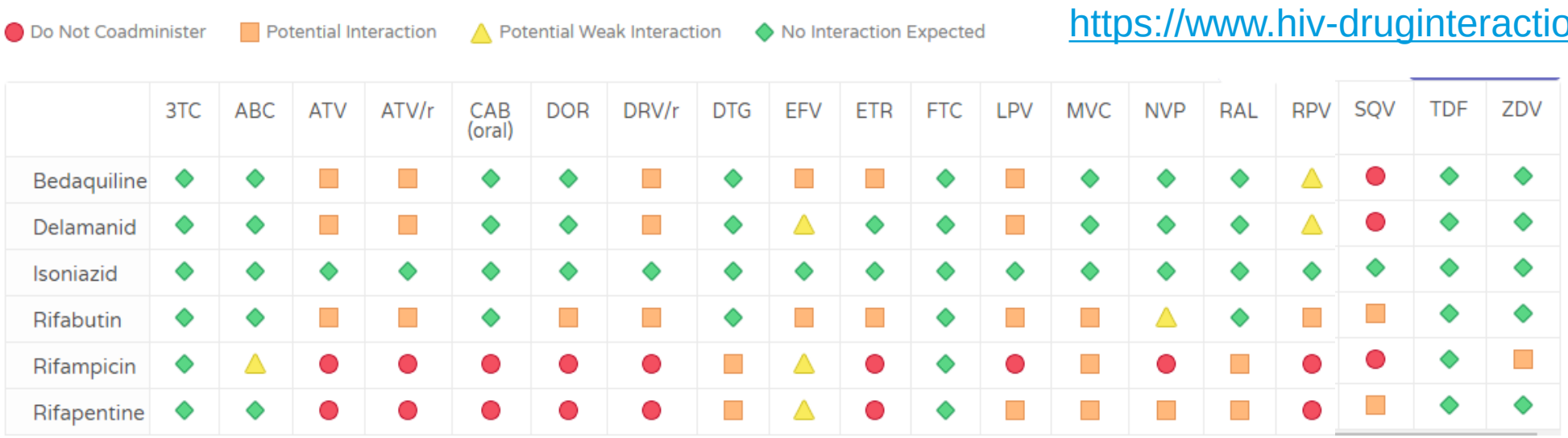
Access to effective ART and anti-TB therapies should be urgently pursued."



Mortality in adults with multidrug-resistant tuberculosis and HIV by antiretroviral therapy and tuberculosis drug use: an individual patient data meta-analysis Gregory P Bisson, MD et al. **Aug 2020**, The Lancet. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31316-7/fulltext

Drug intercations ARVs and new anti-TB medicinces

ARV	Bedaquiline	Delamanid
Efavirenz	Can not be coadministred	No interaction
Niverapine	Lack of information on clear dosage	Possible interaction
Rilpavirine	Assumed no interaction	Assumed no interaction
LPV/r	Increasing BDQ concentrations – may induce toxicity	Increasing BDQ concentrations – may induce toxicity
ATV/r		
DAR/r		
Raltegravir	Assumed no interaction	Not enough studied, assumed no interaction
Dolutegravir		



https://www.hiv-druginteractions.org

New ARVs (BIC and TAF) - good options ?

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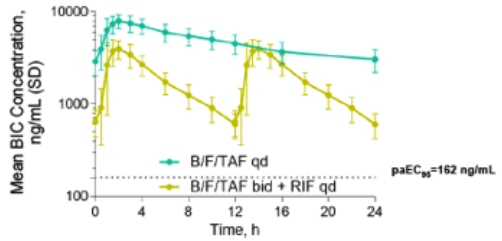
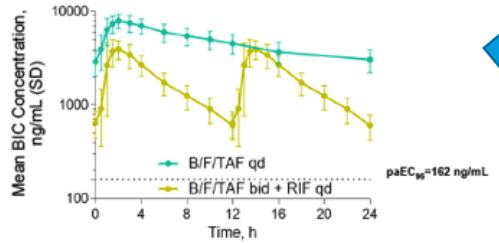
Results: Plasma BIC PK Following B/F/TAF qd vs B/F/TAF bid + RIF qd



BIC PK Mean (%CV)	B/F/TAF qd n=26 (ref)	B/F/TAF bid + RIF qd n=26 (test)	GLSM Ratio (90% CI)
AUC_{0-24}, ng•h/mL	115,000 (21)	45,600 (23)	39.5 (35.7, 43.7)
C_{max}, ng/mL	8530 (16)	4560 (19)	53.2 (49.1, 57.6)

- Daily BIC exposure (AUC_{0-24}) is expected to be ~60% lower following administration of B/F/TAF bid + RIF qd vs B/F/TAF qd

Results: Plasma BIC PK Following B/F/TAF qd vs B/F/TAF bid + RIF qd

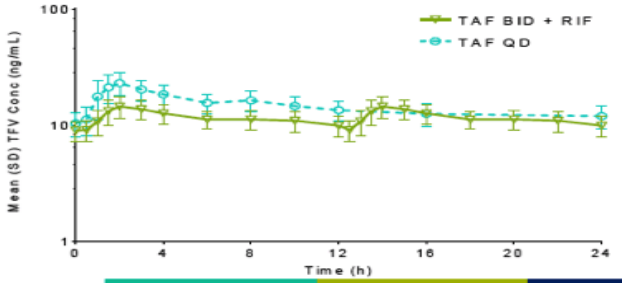


BIC PK Mean (%CV)	B/F/TAF qd n=26 (ref)	B/F/TAF bid + RIF qd n=26 (test)	GLSM Ratio (90% CI)
AUC_{0-24}, ng•h/mL	115,000 (21)	45,600 (23)	39.5 (35.7, 43.7)
C_{max}, ng/mL	8530 (16)	4560 (19)	53.2 (49.1, 57.6)
C_{trough}, ng/mL	3070 (28)	608 (30)	19.7 (17.2, 22.7)

- Daily BIC exposure (AUC_{0-24}) is expected to be ~60% lower following administration of B/F/TAF bid + RIF qd vs B/F/TAF qd
- Following administration of B/F/TAF bid + RIF qd, mean BIC C_t was reduced by ~80% vs B/F/TAF qd

BIC not an option for high burden TB settings where RIF still in use

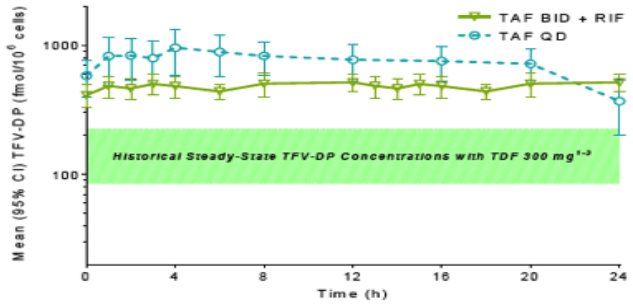
Results: Plasma TFV PK Following TAF BID + RIF vs TAF QD



TFV PK Mean (%CV)	TAF QD n=26 (ref)	TAF BID + RIF n=26 (test)	GLSM Ratio (90% CI)
AUC_{0-24} (ng•h/mL)	348 (20)	277 (19)	79.9 (73.1, 87.3)

- The total overall systemic plasma TFV exposure over 24 hours is expected to be ~20% lower following BID administration of TAF + RIF, versus TAF QD

Results: Intracellular PBMC-Associated TFV-DP Following TAF BID + RIF vs TAF QD



TFV-DP PK	GLSM Ratio (90% CI)
AUC_{0-24} (fmol•h/10^6 cells)	76.3 (58.7, 99.2)

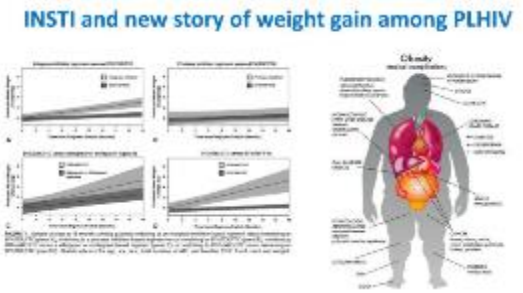
- Following BID administration of TAF plus RIF, the total 24 hour exposure of the intracellular PBMC-associated TFV-DP is expected to be modestly decreased by ~24%, versus TAF QD

1. Pruvost 2007 AAC 2007; 2. Damond JCM 2010; 3. Hawkins JAIDS 2005.

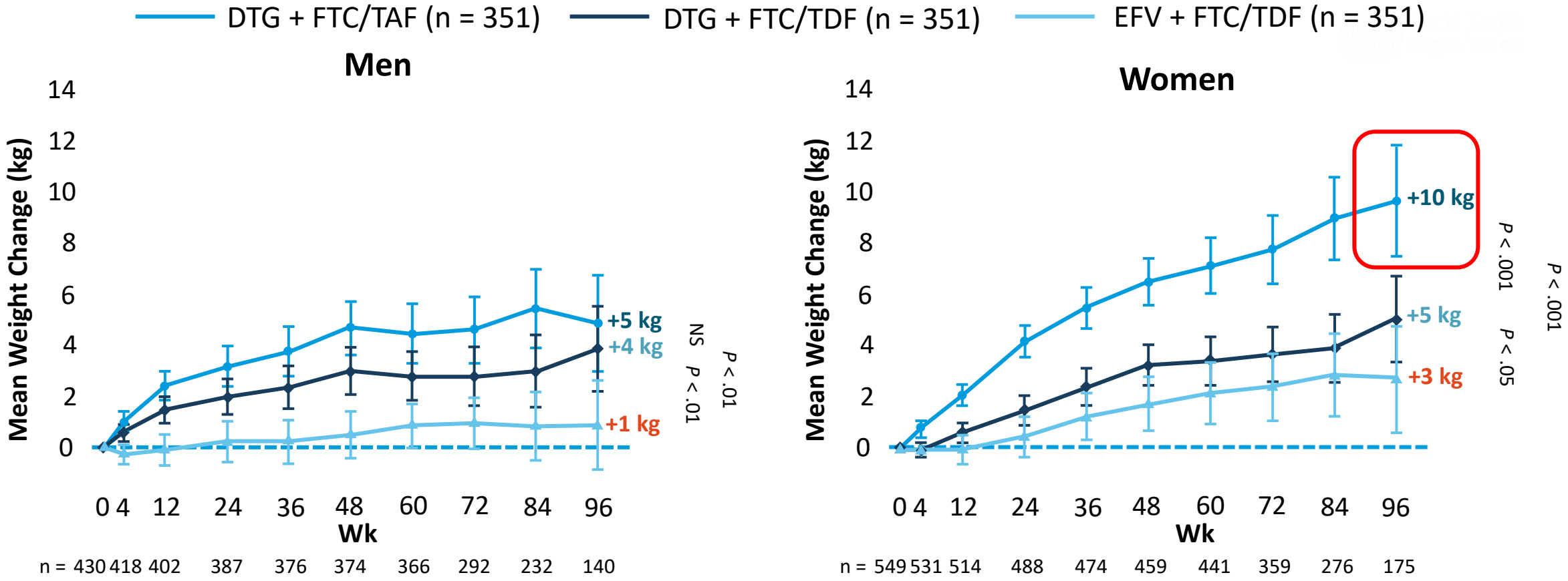
Mind weight gain side effects

ADVANCE: Mean Change in Weight by Sex at Wk 96

Phase III Trial of First-line DTG + FTC/(TAF or TDF) vs EFV/FTC/TDF in SA



Significantly greater weight increase with **DTG** vs **EFV**, with **TAF** vs **TDF** at Wk 96; plateauing in weight gain after Wk 48 observed in men but not in women



Hill. IAS 2019. Abstr MOAX0102LB.

Slide credit: CCO

Higher dose rifampicin in TB/HIV coinfected patients on EFV or DTG

Recent data from CROI-2021
5-10 Mar 2021

- Higher doses of rifamycins may increase efficacy of TB regimens and reduce the required duration for treatment.
- Dose escalation of rifampicin, most used rifamycin, mainly studied in HIV-negative TB patients.
- TB-HIV co-treatment increases risk for drug-drug interactions and drug-related toxicities.

- The study focused on TB-HIV co-infected patients => safety of a higher dose rifampicin and its effect on the pharmacokinetics (PK) of efavirenz (EFV) or dolutegravir (DTG).
- Newly-diagnosed TB patients randomized to either standard (10 mg/kg) or higher (35 mg/kg) dose rifampicin alongside standard TB treatment.
- ART-naïve patients were randomly assigned to DTG- or EFV-based ART regimens.
- Patients on ART (DTG or EFV) at enrolment continued on the same ART regimen however DTG was adjusted from once-daily to twice-daily dosing.
- PK sampling performed at 6 weeks of TB treatment with sampling for DTG 12 hours after the last dose (Ctrough) and a mid-dose concentration was obtained for EFV.
- P-values and 95% CI were obtained using unadjusted linear regression on log-transformed PK values with treatment arm as the only covariate.

- 120 patients enrolled, median age 36 (30-43) years ; 74 (61.7%) were men.
- Geometric mean (95% CI) C12 for DTG were similar in high- and standard-dose rifampicin arms
- Non-significant trend towards lower efavirenz mid-dose concentrations in the high-dose rifampicin arm, but variability was high
- Grade 3-4 adverse events were similar in the high- vs. standard-dose rifampicin
- Sputum conversion at week 8 was higher in high-dose versus standard-dose arms

Compared to the standard dose, **a three-fold dose increase for rifampicin:**

- **did not increase risk of adverse events in patients receiving ART,**
- **appeared to improve TB culture conversion at week 8,**
- **did not alter the magnitude of the drug-drug interaction with DTG.**

High-dose rifampicin interactions with EFV require further exploration.

Table 1: Dolutegravir (DTG) trough and Efavirenz (EFV) mid-dose concentration in patients on high dose vs standard dose rifampicin.

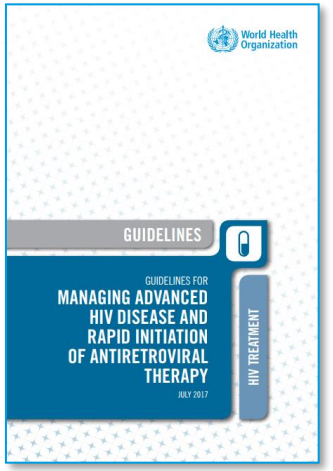
	DTG group		EFV group	
	Arm 1A High dose (RIF 35 mg/kg)	Arm 1B Standard dose (RIF 10 mg/kg)	Arm 2A High dose (RIF 35 mg/kg)	Arm 2B Regular dose (RIF 10 mg/kg)
Number randomized, n	30	34	25	29
PK concentrations				
Geometric Mean	0.32	0.30	0.33	0.60
95% Confidence Interval*	0.11 – 0.95	0.11 – 0.82	0.02 – 4.87	0.06 – 6.02
P-value	0.918		0.72	

RIF – Rifampicin, DTG – Dolutegravir, CI = Confidence interval
DTG concentrations represented as trough drug concentration (C_{trough}) and EFV as mid-dose

Components of package of care interventions for advanced HIV disease (CD4 cell count <200cells/mm3 or a WHO clinical stage 3 or 4 event.)

World Health Organization
REGIONAL OFFICE FOR Europe

Areas for the package	Intervention	CD4 cell count	Adults and adolescents	Children
Screening and diagnosis	Sputum Xpert MTB/RIF as first test for TB diagnosis in symptomatic patients	any	yes	yes
	Urine LF-LAM for TB diagnosis in patients with symptoms and signs of TB	≤100 cells/mm³ Or at any CD4 cell count value if seriously ill	yes	yes*
	Cryptococcal antigen (CrAg) screening	≤ 100 cells/mm³	yes	no
Prophylaxis and pre-emptive treatment	Co-trimoxazole prophylaxis[§]	≤350 cells/mm³ or WHO clinical stage 3 or 4 event. Any CD4 cell count value in settings with high prevalence of malaria and/or severe bacterial infections	yes	yes**
	TB preventive treatment[§]	any	yes	yes#
	Fluconazole pre-emptive therapy for CrAg-positive patients without evidence of meningitis	< 100 cells/mm³	yes	Not applicable (Screening not advised)
	Rapid ART initiation	any	yes	yes
ART initiation	Defer ART initiation if clinical signs and symptoms are suggestive of TB or cryptococcal meningitis	any	yes	yes
Adapted adherence support	Tailored counselling to ensure optimal adherence to advance disease care package, including home visits if feasible	< 200 cells/mm³	yes	yes



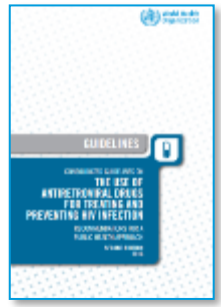
WHO 2017. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy
https://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en/

New consolidated HIV guidelines 2021 (ART)

World Health Organization
REGIONAL OFFICE FOR Europe

HIV GUIDELINES UPDATE ACTIVITIES	TIMELINES
Update of clinical recommendations (use of PoC EID&BH, update of BH algorithm, use of Dapivirine vaginal ring and **timing of ART initiation in TB/HIV coinfection**)	Virtual GDG meeting (28 September-02 October 2020)
Update of recommendations on service delivery (frequency of clinical visits & ART dispensing; approaches for reengagement to care, approaches for measure adherence, specimen collection by lay providers; diagnostic integration across HIV, TB Hep and STIs; integration of HIV/NCD care; integration of HIV/family programme; psychosocial interventions for adolescents with HIV, **TB/HIV treatment linkage interventions**)	Virtual GDG meeting (05-09 October 2020)
Peer review of new clinical and service delivery recommendations and text	October-November 2020
Submission of new recommendations to WHO Guidelines Review Commitee (GRC)	mid-December 2020
Update of the narrative, tables, annexes, references and inclusion of previous 2018/2019 recommendations (i.e., update of chapters on HIV diagnosis, prevention, ART, management of comorbidities & coinfections, service delivery and M&E)	October 2020 – December 2020
WHO GRC approval of updated 2020 recommendations	mid-January 2021
Consolidation of all HIV recommendations (final editing, executive clearance for publication)	January – early February 2021
Release of updated WHO Consolidated HIV treatment Guidelines	Policy briefs **17-18 March**, Guideline **Jul 2021**

Sep 2020



Q1-2 2021

Overall advice/Conclusion:

Simple, affordable and effective programs should be in place in all TB and HIV settings

SIMPLE, AFFORDABLE AND EFFECTIVE HIV/TB PROGRAMMES

All people living with HIV should have access to:

- Antiretroviral Therapy
- TB diagnostics and treatment
- Regular TB screening
- TB preventive therapy (if no TB symptoms)

All people living with TB should have access to:

- HIV testing and antiretro-viral therapy
- TB treatment
- HIV prevention options

WHO HIV Tx App & WHO HTS INFO
Get online with WHO ARV and Treatment and HIV Testing Services Guidelines - 2019

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- https://hivtx.org
- https://hivtx.org/iphone
- https://hivtx.org/android

Electronic versions now *in your hand* !

Acknowledgements:

WHO headquarters, colleagues in WHO EURO

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