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IDSSA

NOVEMBER 2, 2024

ART DRUG CLASSES

VIRAL LOAD

$CD4^+$

DRUG-DRUG INTERACTIONS

Outline

- Part I
  - ART development – a historical timeline
  - Review the HIV life cycle
  - ART classes and place for capsid inhibitors
  - Clinical utility of viral load and $CD4^+$
  - Key principles for drug-drug interactions in HIV management
- Part II
  - Special considerations in chronic conditions, pregnancy and breastfeeding

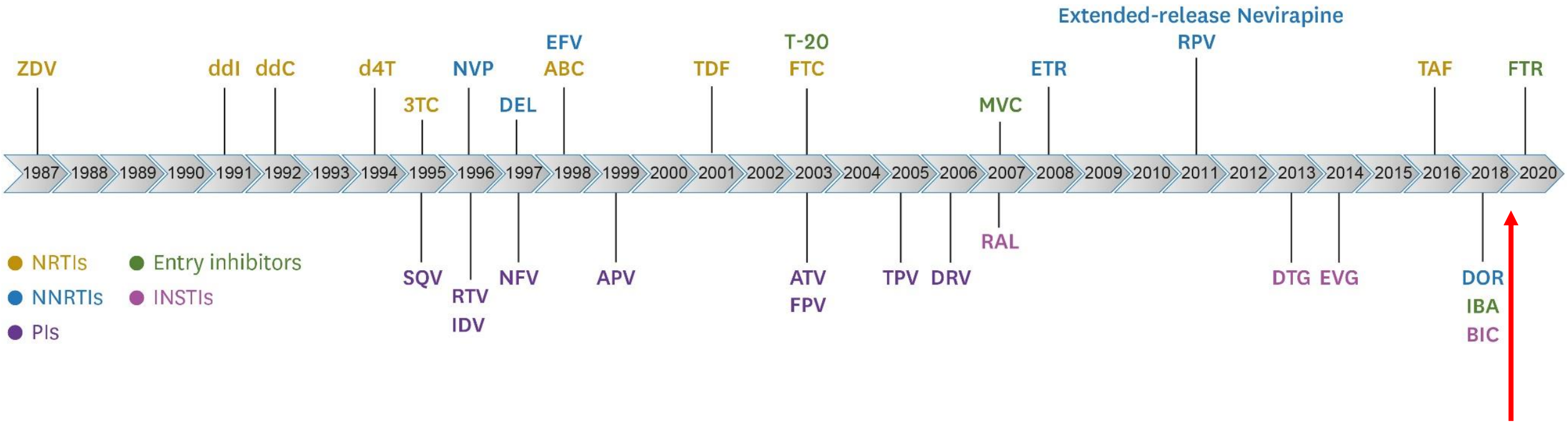
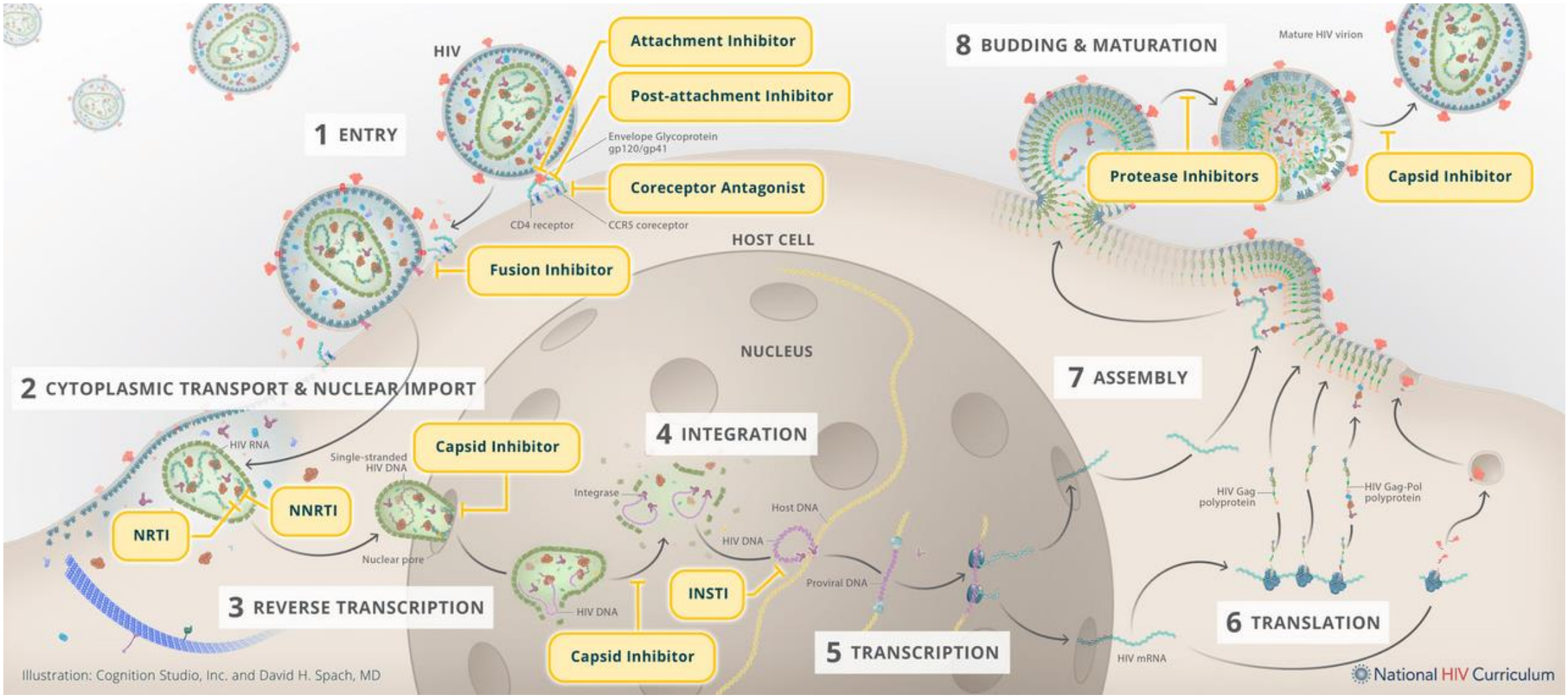


Figure 2. Timeline for FDA-approved antiretroviral drugs

Infect Chemother. 2021 Mar;53(1):29-45.
https://doi.org/10.3947/ic.2020.0100

Current ART Targets



CLASS	TARGET	GENERATION	DRUGS
1. Entry inhibitors: ▪ CD4+ attachment inhibitor ▪ CD4+ post-attachment inhibitor ▪ CCR5 co-receptor antagonist ▪ Fusion inhibitors	▪ HIV envelope: gp 120 ▪ Domain 2 of CD4+ receptor on Th lymphocyte ▪ Host co-receptors: CCR5 ▪ Heptad repeat region of gp 41	First-in-class	▪ Fostemsavir (prodrug) ▪ Ibalizumab (only in iv formulation) ▪ Maravoric (2007) ▪ Enfurvitide (sc injection) (2003)
2. NRTIs (nucleos(t)ide)	▪ HIV reverse transcriptase – act as chain terminators		AZT (1987), ddI (1991), ddC (1992), d4T (1994), 3TC (1995), ABC (1998), TDF (2001), FTC (2003), TAF (2016)
3. NNRTIs	▪ HIV reverse transcriptase – bind to the enzyme rendering it non-functional	▪ 1st generation ▪ 2nd generation	▪ NVP (1996), DLV (1997), EFV (1998) ▪ ETR (2008), RPV (2011)
4. INSTIs	▪ HIV integrase	▪ 1st generation ▪ 2nd generation	▪ Raltegravir (2007), Elvitegravir (2012) ▪ Dolutegravir (2013), Bicetegravir (2018), Cabotegravir (injectable) (2021)
5. PIs	▪ HIV protease	▪ 1st generation ▪ 2nd generation ▪ 3rd generation ▪ 4th generation	▪ SQV, RTV, NFV, IDV, APV ▪ LPV, FPV, ATV ▪ TPV ▪ DRV
6. Capsid inhibitors	▪ HIV capsid	First-in-class	Lenacapavir
7. Pharmacokinetic boosters	▪ HIV protease ▪ Human cytochrome P450 3A enzyme	N/A	▪ Ritonavir ▪ Cobicistat

ARVs In Clinical Practice – Treat HIV

- HAART = 3 drugs
  - 2 fully active* + 1 w/ high genetic barrier
    - Back-bone = x2 NRTIs
    - Anchor = x1 INSTI or boosted PIs or NNRTIs
  - Non-inferior dual regimens
    - Raltegravir plus DRV/R
    - Lamivudine plus DTG
      - Avoid in VL ≥ 500,000 cpml and/or HBV co-infection
  - Avoid NNRTIs and fusion inhibitors in HIV-2

- Regimens to avoid when baseline VL >100,000
  - Anchored by Rilpivirine
  - ABC/3TC plus EFV or ATV/R
- Avoid
  - Low potency regimens: NNRTI anchor, dual or triple NRTI, unboosted PI
  - Toxic combinations: TDF/ddI, d4T/AZT
  - DRV/r in sulphur allergy
  - NVP in $CD4^+$ >250 (F) and >400 (M)
  - RTV+cobicistat, 3TC+FTC, TAF+TDF
  - Full-dose RTV

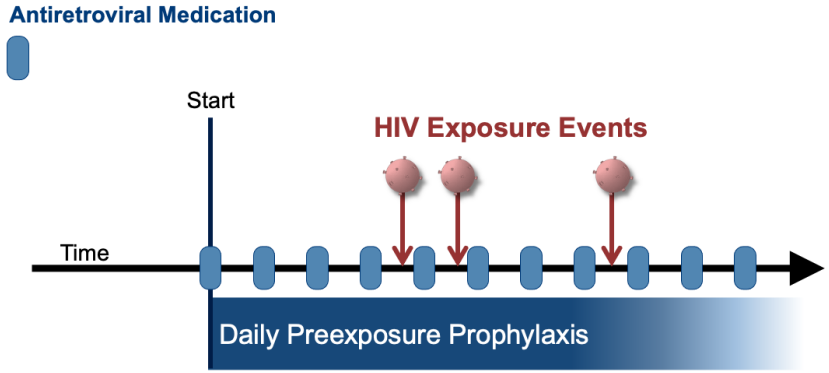
**NADIA, ERNEST, VISEND, ARTIST → recycling of not-fully active NRTIs can still be efficacious (TDF/3TC and AZT/ 3TC backbone*

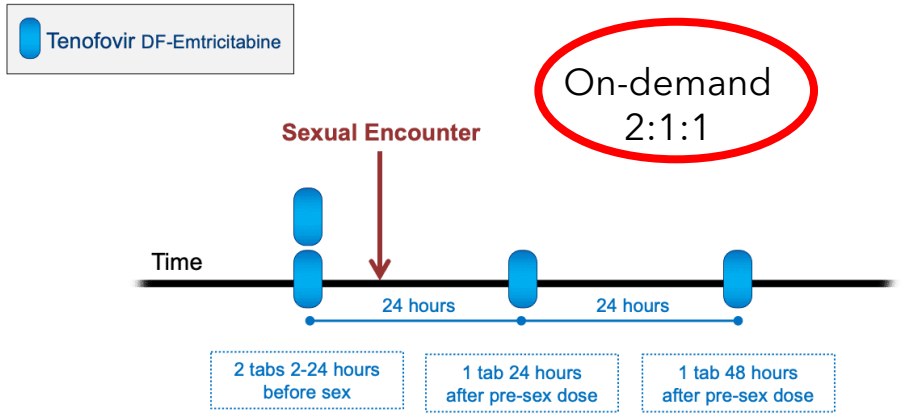
ARVs in Clinical Practice – Prevent HIV

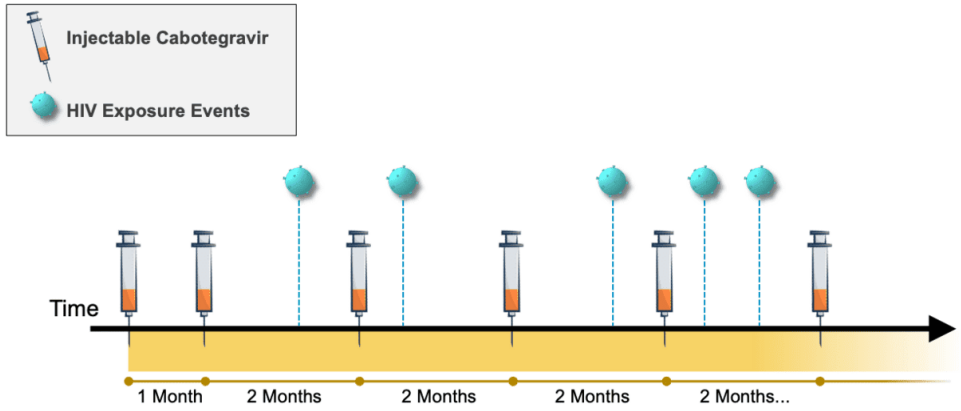
- PEP – x 28d
  - X3 drugs as per Rx for HIV
    - ❑TDF/TAF + 3TC/FTC + DTG/BIC/RAL or DRV/r
    - ❑Less desirable: AZT, LPV/r, ATV/r
  - Avoid: ABC, d4T, 1st gen PIs, NNRTIs, Maravoric

- PrEP – not for those w/ HBV infection
  - TDF/FTC, TAF/FTC, CAB-LA
  - Daily vs on-demand

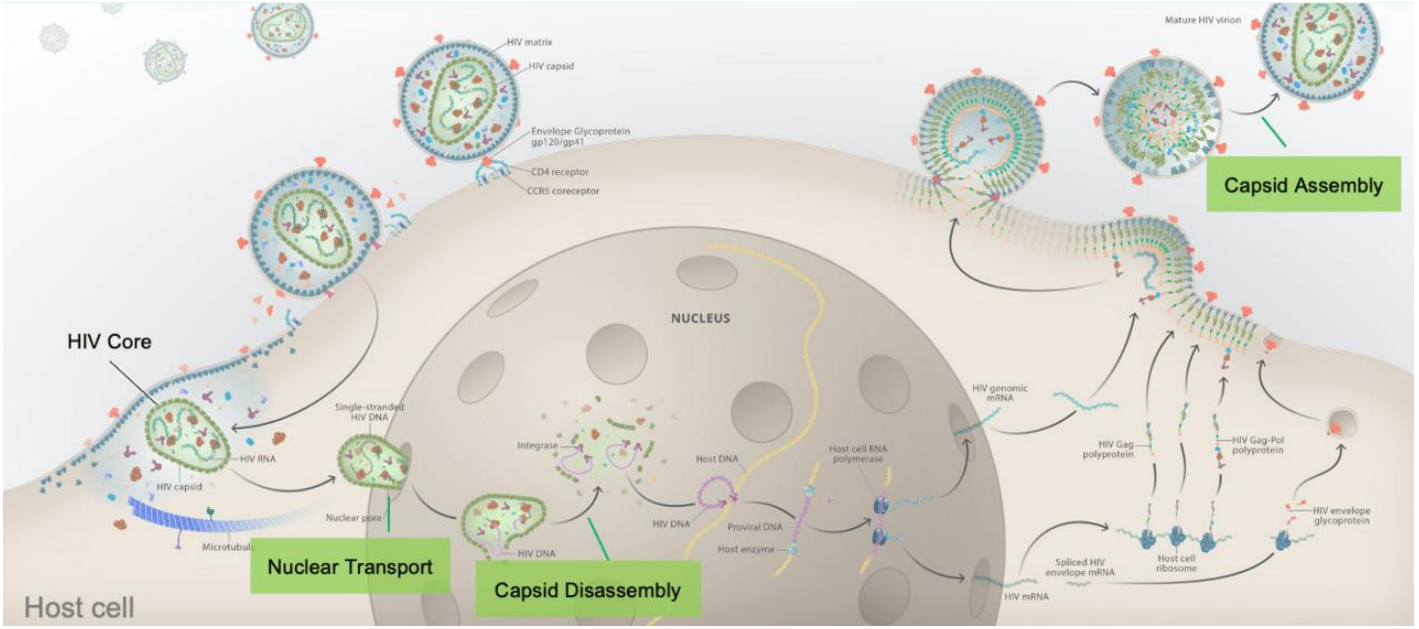
- TasP – ART in PMTCT to protect neonate and infant, U=U (i.e. VL<50 for ≥6mo, sexual transmission)







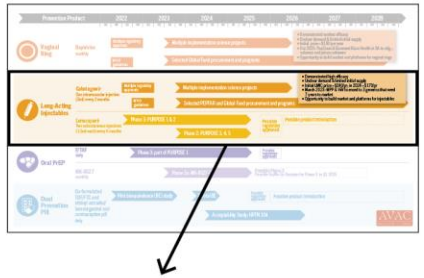
Capsid Inhibitors – Lenacapavir



- Binds between subunits of capsid proteins reducing flexibility of intra- and inter-hexamer connections
- Inhibits viral replication at 3 steps in HIV life cycle:
  1) Disrupts normal transport of capsid core through nuclear pore complex
  2) Prevents uncoating or disassembly of the capsid
  3) Interferes w/ reassembly of capsid core during maturation

Overview of Lenacapavir (LEN) for PrEP Trials

- Initial data
- Possible data
- Possible earliest regulatory submissions
- Possible earliest regulatory approval and market entry with product from Gilead
- Possible earliest generic manufacturer(s)

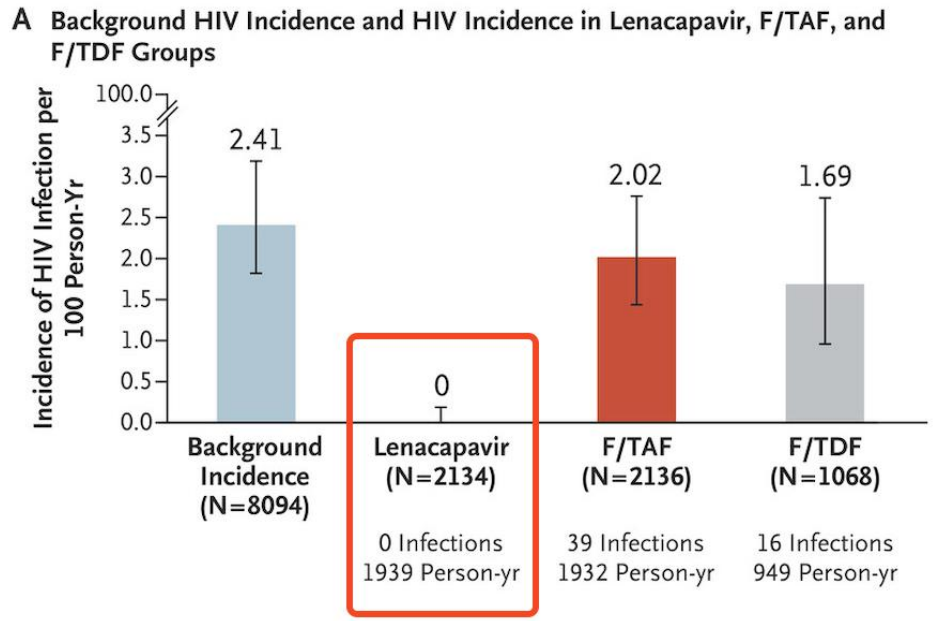


Trial	Population	Location	Size	2022	2023	2024	2025	2026	2027	2028
PURPOSE 1 Phase 3 Injectable lenacapavir & oral F/TAF	Cisgender adolescent girls and young women	South Africa and Uganda	**5,010**	Initial results released in June 2024 demonstrated no infections in the LEN arm						
PURPOSE 2 Phase 3 Injectable lenacapavir	Cisgender men who have sex with men, Transgender women, Transgender men, Gender non-binary	US, South Africa, Peru, Brazil, Mexico, Argentina, and Thailand	**3,000**	Initial results released in September 2024 demonstrated LEN reduced HIV infections by 96% compared to background HIV incidence						
PURPOSE 3 **HPTN 102** Phase 2 Injectable lenacapavir	Cisgender women	US	**250**			Currently recruiting; estimated study completed date early 2028				
PURPOSE 4 **HPTN 103** Phase 2 Injectable lenacapavir	People who inject drugs	US	**250**				Currently recruiting; estimated study completed date mid-2027			
PURPOSE 5 Phase 2 Injectable lenacapavir	Cisgender men who have sex with men, Transgender women, Transgender men, Gender non-binary	France and UK	**262**				Enrollment expected to begin in the second half of 2024			

AVAC
Advocacy. Access. Equity.

Updated September 2024

PURPOSE-1



- Adolescents and young women ≥16y - ≤25y
- Randomized, double-blind, placebo
- Interventions:
  - Lenacapavir 927mg sc day 1 and after 26w plus LD 600mg po day 1 and 2
  - TAF/FTC 25mg/200mg
- Two comparison groups
  - Active control: TDF/FTC 300mg/200mg
  - Cross-sectional incidence cohort
- 25 centers South Africa, 3 Uganda

VIRAL LOAD

CLINICAL UTILITY

Viral Load in Clinical Practice

- VL = concentration of free HIV-1 in plasma
- 3 types of VL tests: quantitative PCR, nucleic acid sequence-based assay, branched-chain DNA assay

1. Confirming HIV infection
    - Acute HIV
    - HIV-exposed neonate and infant (qualitative PCR)
    - Equivocal rapid results
        - NB: Eclipse phase of HIV – no test can detect HIV during d1-10 post-exposure
    - Clients who have been on PrEP – may have false negative antibody tests
2. Monitoring response to ART - most important predictor of overall successful Rx outcome
    - Target → VL <50 by 6mo (virologic suppression as early as 4w w/ INSTI anchored regimen)
    - Small fluctuations (≤ $\log_{10}$ 0.3 change) not clinically significant

Point-of-Care VL Tests

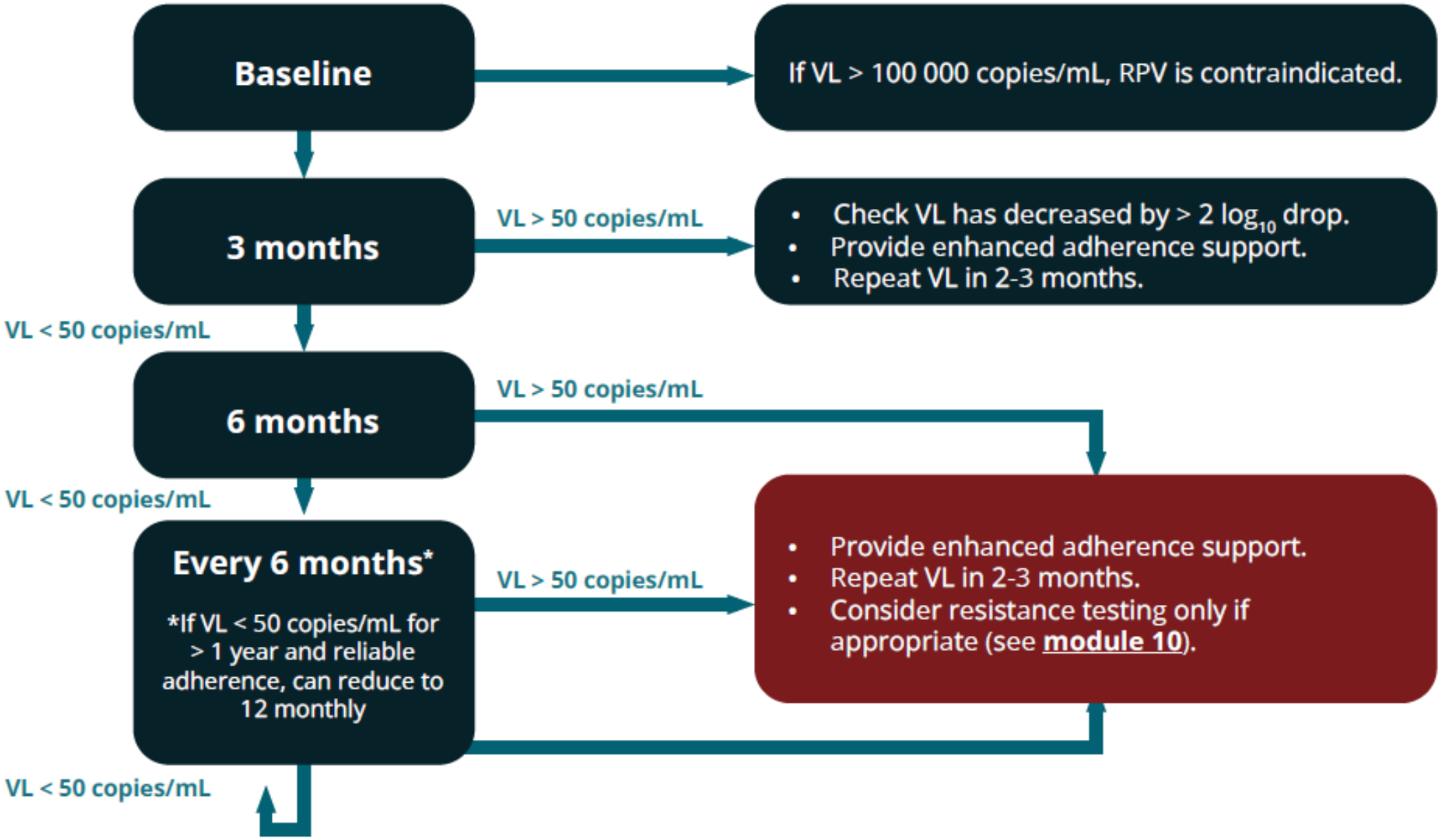
- WHO prequalified two tests
  - Cepheid Xpert HIV-1 VL assay
  - Abbott m-PIMA
- Benefits
  - More rapid testing and return of results (2h)
  - Fewer clinic visits for results
  - ↑ likelihood of clinical action following ↑ VL
  - ↑ likelihood of long-term VL suppression, retention in care
  - Facilitates transfer to differentiated care for those w/ VL <50
  - More reliable timing and recording of test results

Box 4.5. Priorities for point-of-care viral load testing

The following populations should be given priority for point-of-care viral load testing:

- Pregnant and breastfeeding women
- Infants, children and adolescents
- People requiring a repeat viral load after a first elevated viral load
- People for whom treatment failure is suspected
- People presenting sick, living with advanced HIV disease or having a known opportunistic infection (TB, cryptococcal infection, etc.)
- First scheduled viral load test for people re-entering care

WHO 2021


Baseline
If VL > 100 000 copies/mL, RPV is contraindicated.
3 months
VL > 50 copies/mL
Check VL has decreased by > 2 log10 drop.
Provide enhanced adherence support.
Repeat VL in 2-3 months.
VL < 50 copies/mL
6 months
VL > 50 copies/mL
VL < 50 copies/mL
Every 6 months*
*If VL < 50 copies/mL for > 1 year and reliable adherence, can reduce to 12 monthly
VL > 50 copies/mL
Provide enhanced adherence support.
Repeat VL in 2-3 months.
Consider resistance testing only if appropriate (see module 10).
VL < 50 copies/mL

VL Results

- Virological failure criteria:
  - On ART at least 6mo
  - x2 consecutive VL >1000 2-3mo apart with adherence support following first VL
    - ❑ Refers to VL taken after ≥2 years on INSTIs
- Viral blips
  - Isolated VL 50-999 followed by undetectable VL
  - Causes: intermittent adherence, acute illness, DDIs
  - Not consequential but aetiology must be explored
- VL $\log_{10}$ change >0.5 = 3-fold change → clinically significant in either direction (suppression or failure)

$\log_{10}$ Values of VL Changes	
Fold Change in VL	$\log_{10}$ Change
2	0.3
3	0.5
5	0.7
10	1.0
100	2.0
1000	3.0

Handbook HIV Medicine 3rd ed

Responding To VL

- <50
  - Clinically stable → maintain on current ART regimen and recheck in 12mo
- 50-999
  - >1 value predictive of future virological failure
  - Associated w/ new DR mutations (esp regimens anchored by NNRTI, PI, RAL)
  - Unclear if clinically relevant for DTG regimens
  - Enhanced adherence support, repeat VL in 3 mo, keep on same ART regimen
- >1000
  - NNRTI anchor → x1 result warrants a switch
  - PI or INSTI anchor → follow guideline algorithm
    - ❑ Enhanced adherence support +/- resistance testing and ART switch

VL <50 does not mutate and develop resistance

U=U
(sexual transmission route)

Responding To VL >50

1. Determine if viral blip or potential failure/resistance
2. Initiate enhanced adherence
   - Measures: pharmacy refills, attendance at scheduled appointments, TDM. Not self-report.
3. Correctly classify if patient on TLD1 or TLD2 or TLD3
   - NB: Vertical transmission adolescents, patients re-engaging in care, potential DDI w/ DTG → TLD2
4. Confirm eligibility for resistance testing
   - VL failure on TLD2 or TLD3 for ≥2y ***plus*** measured adherence must be at least 80%

Transmitted resistance as a risk for failure

Rare overall

Unlikely on regimens anchored by DTG

Possible on regimens anchored by NNRTI (K103N mutation) – i.e. NVP or EFV, but not RPV or ETR

Special Populations

Elite controllers

- About 0.5% of HIV population
- Durable natural control of HIV w/out ART
- VL undetectable
- Usually maintain $CD4^+$ >500 long-term

Viraemic controllers

- Larger sub-set of HIV population
- Naturally maintain low, but not undetectable, VL w/out ART
- $CD4^+$ less stable & lower on average

- ❑ Risk of forward transmission of HIV
- ❑ Non-HIV-related morbidity due to chronic immune activation
- ❑ Significant proportion eventually lose immunologic control and experience disease progression

Treat all VC according to national guidelines for PLWH
Offer ART to all EC for benefits of ↓sing potential non-HIV-related morbidity (atherosclerosis)

CD4+

Clinical Utility

Role of CD4+ Testing

Staging and risk assessment at entry into care

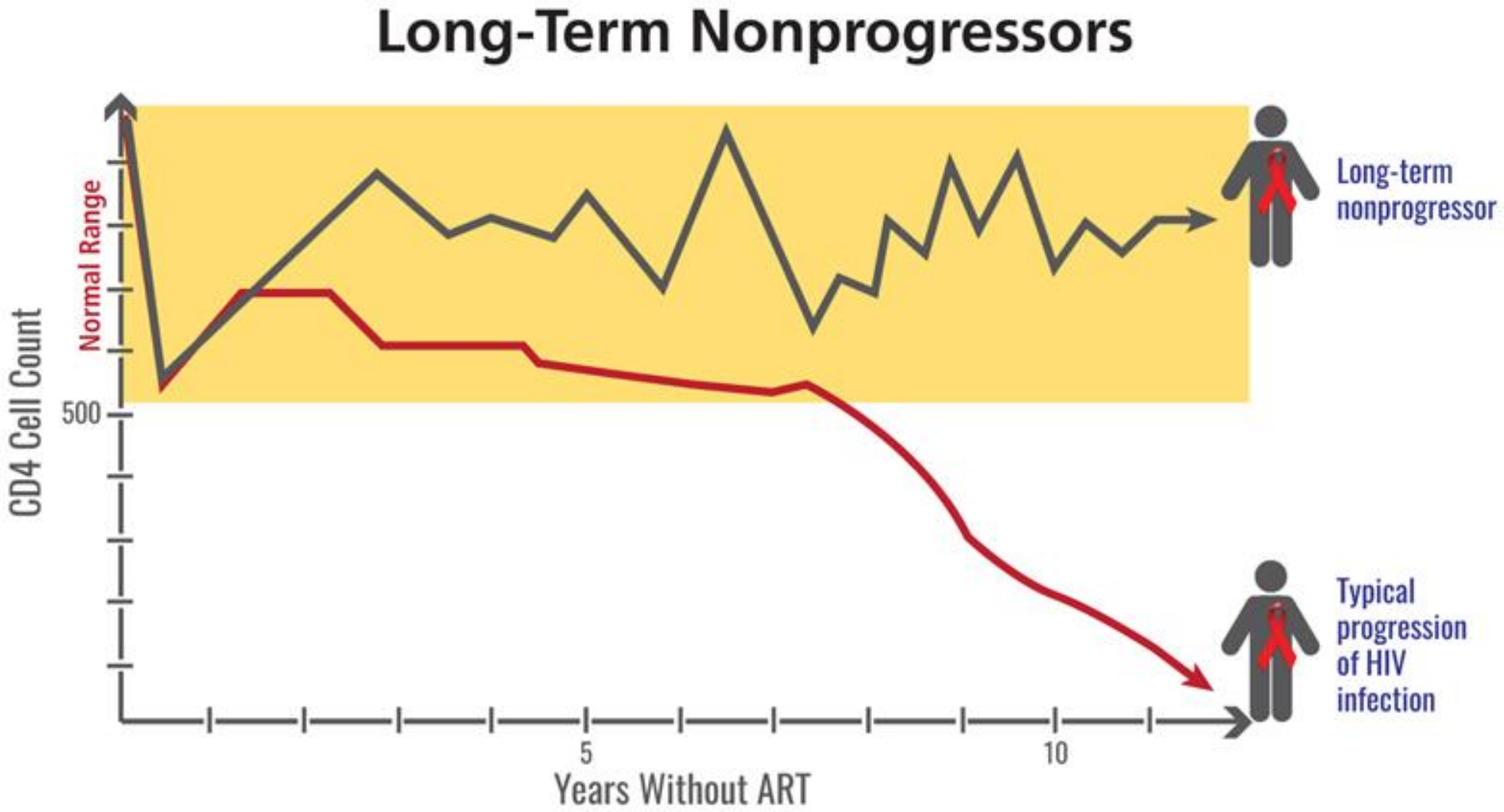
Screen for opportunistics: clinical, lab reflex tests

Initiate appropriate antimicrobial prophylaxis

Evaluate IRIS risk

Predict trajectory of CD4+ response on effective ART

- Typical schedule
  - Baseline
  - Q6mo until CD4+ >200
  - No further monitoring if clinically stable and virally suppressed
  - Re-start schedule
    - ❑ Clinical failure (new or recurrent WHO stage 4 but also stage 3 TB and serious bacterial infection – differentiate from IRIS)
    - ❑ Virological failure



CD4⁺ count is the strongest predictor of HIV progression

https://clinicalinfo.hiv.gov/

CD4+ Response To ART

- CD4+ recovery phases
  - Brisk increase in first 6mo due to release of memory CD4+ cells trapped w/in lymphoid tissue
  - Gradual increase over 3-6y: naive CD4+ cells in thymus and memory CD4+ cells

- Expected: 50-150 increase in first year
- Thereafter, annual increase of 50-100 until steady state

- Best opportunity for maximal CD4+ recovery: recent HIV acquisition plus early ART
  - 15-20% patients who initiate ART at CD4+ <200 plateau at abnormally low CD4+ counts despite virologic suppression
    - ❑ Recovery may be so slow, up to 10 years

Discordant $CD4^+$/VL Response

- Definition: $CD4^+$ <200 plus undetectable VL for ≥2y
- Associated w/ both HIV and non-HIV morbidity and mortality (2.6-fold greater risk)
- Potential causes:
  - Pre-treatment $CD4^+$ <200
  - Age
  - Myelosuppressive drugs (affect absolute count more than $CD4^+$%)
  - Infections: TB, hepatitis C, HIV-2 co-infection
  - Malignancy: lymphoma
  - Medications: steroids
  - Auto-immune disease: SLE

Immunologically discordant response does not imply Rx failure

STEPS TO FOLLOW

- Comprehensive history: new illness, new therapies
- Confirm and maintain both clinical and virological success
- Adaptive adherence support
- Appropriate screening, prophylaxis and pre-emptive therapy
- Manage modifiable risk factors for chronic disease
- BMAT if pancytopenia, B symptoms, HSM

Figure 3 outlines the suggested approach to patients with low CD4+ counts despite a suppressed viral load on ART.

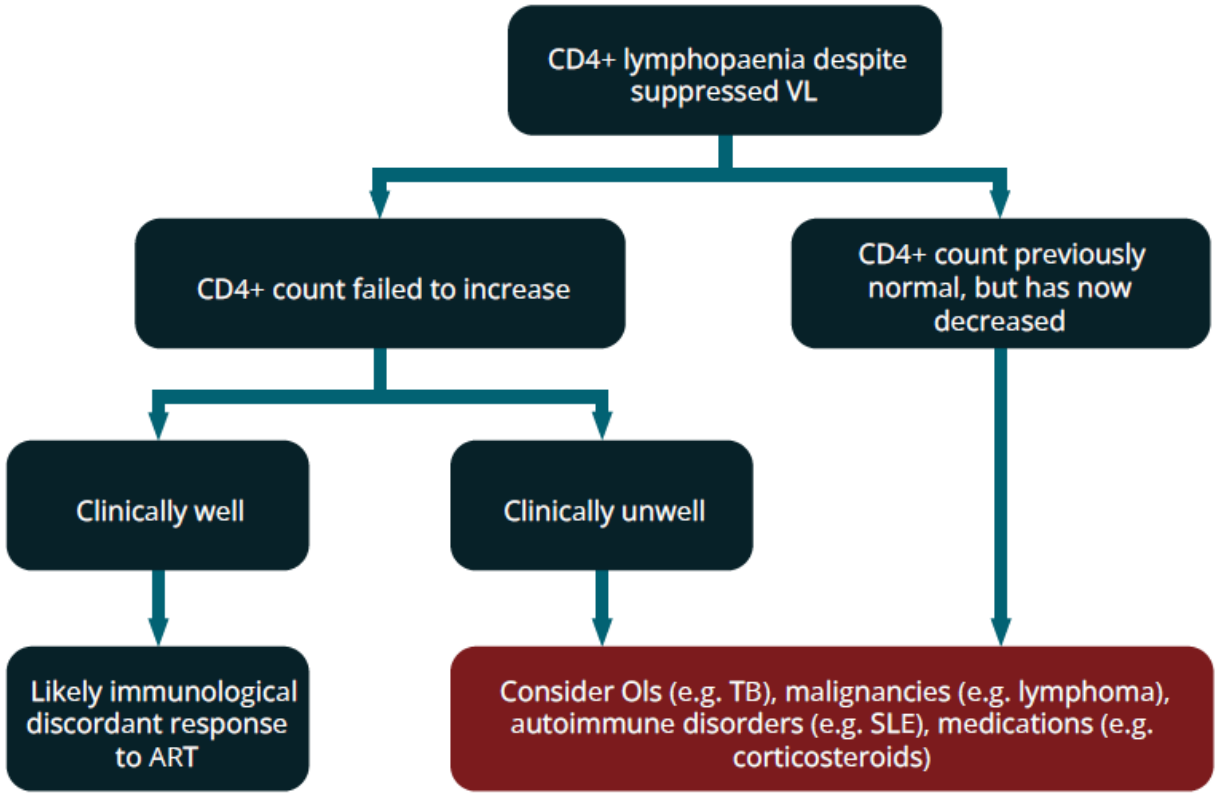


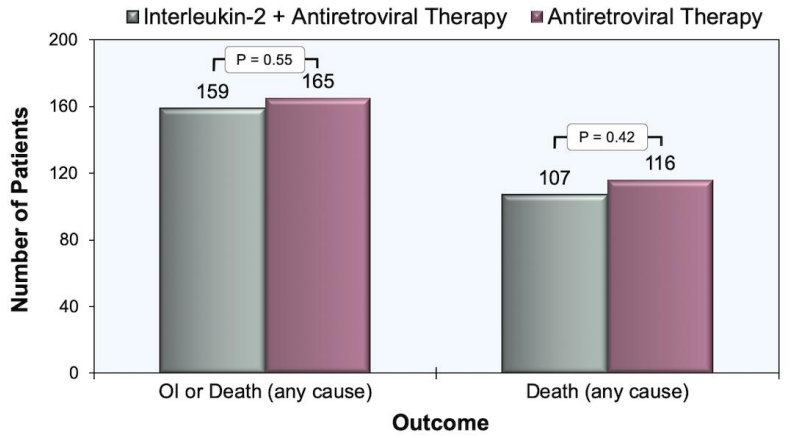
FIGURE 3: Suggested approach to patients with low CD4+ counts despite a suppressed viral load on ART.

(ART; antiretroviral therapy; CD4+, cluster of differentiation 4; OIs, opportunistic infections; SLE, systemic lupus erythematosus; TB, tuberculosis; VL, viral load).

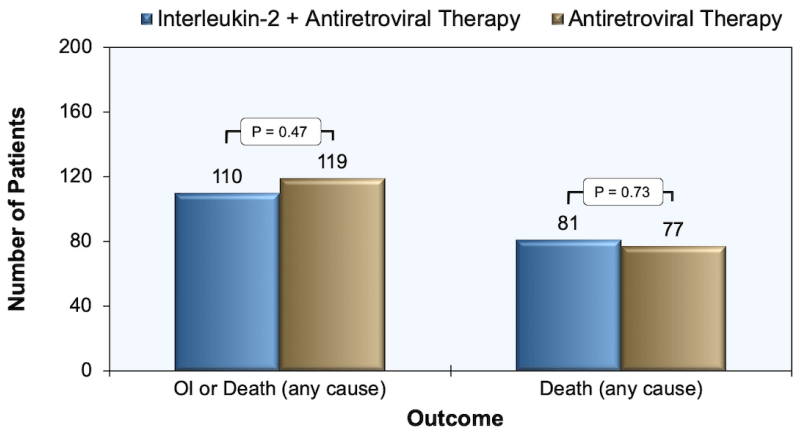
SAHCS Adult ART 2023

Persistent CD4+ Lymphopaenia

- Ineffective strategies for mortality and reduction in OI incidence outcomes
  - ART intensification
  - Switching ART classes
  - IL-2 therapy to raise CD4+ count and ↓ inflammation
  - IL-7 therapy
  - Growth hormone
  - Monitoring immune activation and inflammatory markers
- IL-2 trials – significant CD4+ rise but no impact on clinically meaningful outcomes



ESPRIT



SILCATT

Drug-Drug Interactions

Key Principles

There's Always A Chronic Meds List

- ART regimen
  - Individual drugs or FDC
- *Plus* meds for
  - Opportunistic conditions
  - OI prophylaxis
  - Non-HIV co-morbidities: chronic pain, HPT, DM, epilepsy, autoimmune disease, viral hepatitis etc
  - Complementary meds: OTC supplements, herbal and traditional remedies (often not disclosed)
  - Acute infections
- *Plus*
  - Food requirements/rules
- *Plus*
  - Multiple and/or duplicate scripts from different healthcare settings

Risk Factors for DDIs

- Long-standing illness, chronic conditions or disability
- Age ≥50y
  - Emerging chronic illnesses in aging population: HPT, DM, COPD
  - Age-related physiological changes that alter drug responses in older individuals
- Rx provided by ≥1 care provider including specialists
- Limited care provider communication
- Prescriptions filled at multiple pharmacies
- Recent hospitalization
  - Medication changes due to AEs, DDIs, formulary switches, out-of-stocks
  - Medication errors on discharge: duplications, omissions, or combinations that introduce new DDIs

Anticipate DDIs

- Polypharmacy is common especially as patients age
  - No clear universal definition but most studies = regular use of ≥5 meds at the same time
  - Can be appropriate or inappropriate
- Potential DDIs can:
  - Be clinically significant or insignificant
  - Have predictable or unpredictable consequences
  - Be adverse: sub-therapeutic drug concentrations → Rx failure, toxicity
  - Be beneficial
- Two problematic ART classes: PIs and NNRTIs
  - INSTIs and NRTIs – less implicated
- Genetic polymorphisms and variant alleles that alter drug metabolism – wide variability in population

DDI Mechanisms

1. Pharmacodynamic
   - Direct effects of interacting drugs plus changes in patient response to the drugs
     - Drug action at receptors: pure or partial agonists or antagonists
       - Competition at receptor sites, and/or activity of ≥2 drugs on same physiological system
       - Effects – additive/dose-dependent, synergistic or antagonistic
         - E.g. AZT, ganciclovir, ribavirin → myelosuppression
2. Pharmacokinetic
   - Modification of ADME
     - Absorption: gastric pH (ATV), chelation (DTG), GIT motility
     - Distribution: competitive protein-binding
       - Rarely clinically significant due to rapid equilibrium, except for drugs w/ narrow therapeutic window

DDI Mechanisms

- Metabolism – liver major site
  - Phase I: oxidation, reduction, hydrolysis by CYP P450 system of isoenzymes in liver, enterocytes
    - 3 families: CYP1, CYP2, CYP3 → sub-families → isoenzymes
      - ✓ Major system = CYP3A4 → metabolises about half of drugs exposed to P450
    - Drugs are substrates, inducers or inhibitors of P450
  - Phase II: altered drug conjugation
    - E.g. enzyme uridine diphosphate glurunosyltransferase (UGT) conjugates DTG while Rifampicin induces UGT
- Excretion: kidney major site → can be active or passive
  - Competitive inhibition of tubular secretion via drug transport proteins
  - Urine pH alterations affect rate of drug elimination: probenecid and penicillins

DDI Mechanisms

- P450 inhibition
  - Direct competition
  - Usually involves ≥1 CYP isoenzymes
  - Rapid onset and rapid decay once inhibiting drug is metabolized
- P450 induction
  - Upregulation of many CYP genes, drug transporters and conjugating enzymes
  - Leads to increased enzyme expression
  - Develops slowly & wanes slowly – maximal at 14d & disappears slowly over 14d

- Modification of drug transporters
- Sites: liver, kidney, small intestine, blood-tissue barriers
- E.g. P-glycoprotein
  - Transmembrane efflux pump – active drug transport
  - Absorption – brush border of enterocytes
  - Excretion – canalicular surface of hepatocytes and apical surface of proximal tubular kidney cells
- Other families: MATE, OCT, OAT, OATP, BCRP

**St. John's wort – potent inducer of CYP3A4 and P-gp*

Harnessing Benefits of DDIs

- PD synergy
  - Combination of ≥2 drugs in which shared effect is > effect of individual drugs
  - ART, RHZE etc

- PK boosting
  - Involves inhibiting P450 or drug transporters to ↑ bioavailability of 2nd co-administered drug
  - Facilitates less frequent dosing intervals, lower dosing, ↓AEs, improved adherence
    - Potent CYP3A4 inhibitors: ritonavir, cobicistat
    - Potent organic anion transporter inhibitor: probenecid

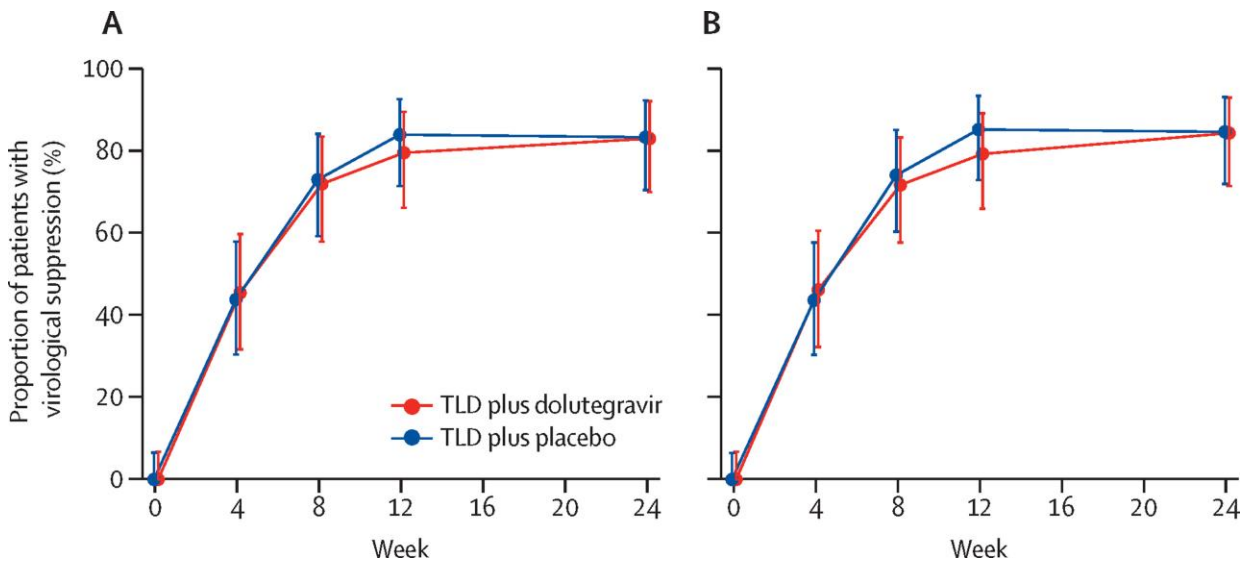
When simplifying or changing ART regimens, important to identify potential effects a loss (or gain) of *CYP inhibition* may have on *every drug* (not just ARVs) that an individual is taking

Common Interactions in Clinical Practice

ATV and gastric pH (PPI, antacids)	Rifampicin and DTG	DTG and polyvalent cations	Aminoglycosides and TDF	Amlodipine and PIs	EFV and Bedaquiline	NVP and dexamethasone
Statins and PIs	Rifampicin and PIs	DTG and Atenolol	TDF and Lithium	Rifabutin and Fluconazole	NVP and Rifamycins	SSRIs and PIs
St. John's wort and everything	Rifapentine and PIs	DTG and Metformin	TDF and Hep C DAAT	Rifabutin and PIs	NVP and hep C DAAT	DTG and ETR without boosted PI
DRV/r and suphur allergy	Rifampicin and NNRTIs	AEDs and DTG	Colchicine and PIs	Low-dose COCs and PIs	Quetiapine and PIs	Midazolam and PIs

Rifampicin Plus DTG

RADIANT (Phase 2b RCT Cape Town 2023)



A= mITT, B = per protocol

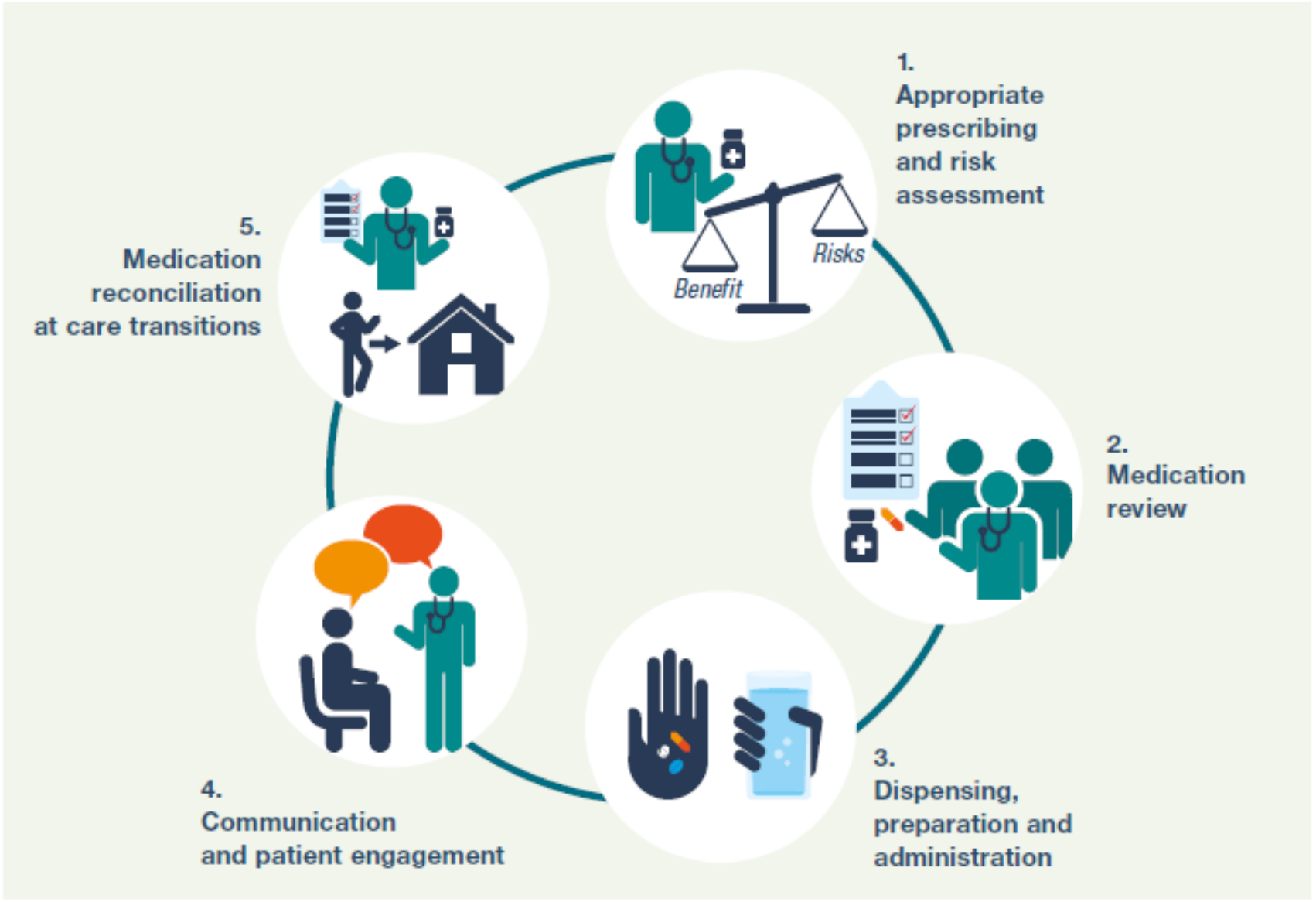
Griesel, Rulan et al. The Lancet HIV, Volume 10, Issue 7, e433 - e441

BOTSWANA (Retrospective cohort 2019)

Characteristic		TB treatment success n/N (%)	Viral load suppressed n/N (%)
Age	≤ 30	199/228 (87.3)	129/143 (90.2)
	31-40	430/469 (91.7)	307/317 (96.8)
	41-50	289/319 (90.6)	187/200 (93.5)
	> 50	183/209 (87.6)	131/137 (95.6)
Gender	Female	502/555 (90.5)	339/360 (94.2)
	Male	599/670 (89.4)	415/437 (95.0)
Dolutegravir	No DTG	429/486 (88.3)	288/307 (93.8)
	50 mg OD	298/322 (92.6)	204/214 (95.3)
	50 mg BD	352/390 (90.3)	241/254 (94.9)
	Missing dosage	22/27 (81.5)	21/22 (95.4)
CD4 (cells/ml^3)	≤ 100	100/129 (77.5)	64/77 (83.1)
	101-200	157/169 (92.9)	116/124 (93.5)
	201-350	261/279 (93.6)	207/217 (95.4)
	> 350	378/410 (92.2)	302/309 (97.7)
	Missing	205/238 (86.1)	65/70 (92.9)
TB site	Pulmonary	739/799 (92.5)	466/497 (93.8)
	Extrapulmonary	171/203 (84.2)	118/122 (96.7)
	Both	7/8 (87.5)	3/4 (75.0)
	Missing	183/215 (85.1)	161/174 (92.5)

IQR=Interquartile range

Figure 1. Key steps for ensuring medication safety



https://www.who.int/docs/default-source/patient-safety/who-uhc-sds-2019-11-eng.pdf

Liverpool Drug Interactions

HIV Hepatology COVID-19 Cancer

www.druginteractions.org

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0800 212 506

USEFUL RESOURCES

- https://reference.medscape.com/drug-interactionchecker
- https://hivclinic.ca/drug-information/drug-interaction-tables/
- https://www.webmd.com/interaction-checker/default.htm
- https://clinicalinfo.hiv.gov/en/drugs

MEDICINES INFORMATION CENTRE

CALL US ON
021 406 6829
FOR FREE MEDICINE-RELATED QUERIES
For HIV/TB cases: 0800 212 506
The service is limited to healthcare workers

NATIONAL HIV & TB HEALTH CARE WORKER HOTLINE
0800 212 506

CHRONIC CONDITIONS

PREGNANCY

LACTATION

DR. KYAZZE

IDSSA

NOVEMBER 2, 2024

When effective treatment of incurable diseases extends life expectancy and causes symptom remission, acute and terminal illness models must be replaced by a chronic care model (CCM) in which patient self-management is a key component

Bodenheimer et al 2002

Chronic Diseases and HIV

Chronic Conditions

- Broadly defined as conditions lasting ≥1 year that require medical attention and/or limit ADLs

- With HAART → HIV now part of chronic disease spectrum
  - Demographic shift – increasing proportion of PLWH >50y

- Risk for multimorbidity is present across all age groups
  - May be pre-existing, HIV-related or due to ageing
  - High degree of shared risk factors
  - Accentuated and accelerated → younger age onset
  - Have implications for treatment, health outcomes and functional status
  - Often stigmatised
- Can complicate HIV management increasing MnM

- Understanding how chronic conditions distribute or co-occur among PLWH essential for targeted interventions – research and policy

Clin Infect Dis 2014, Dec 15;59(12):1787-97. doi: 10.1093/cid/ciu70

Interface Between HIV and Chronic Disease

- HIV+ individuals at ↑ risk for chronic conditions > general population
  - Ageing, direct effects of HIV, ART side effects, high-risk sexual behaviour, intimate partner violence
  - Often comorbidities – CVD, DM, CKD, liver disease, cancer, mental health disorders
- Multiple mechanisms in HIV/chronic diseases
  - Immune dysfunction → ↑ vulnerability to recurrent infections, malignancy, autoimmune disease
  - Chronic inflammation from persistent immune activation → accelerated atherosclerosis, CVD, CKD
  - Metabolic changes due to HIV and ART → ↑ risks of obesity, insulin resistance, dyslipidaemia
  - Disability as part of disease sequelae → CVA, CCF, lung fibrosis, neurocognitive disorder

HIV and Aging NIH 2020

Management Principles

Interactions

- DDIs → ART and chronic condition scripts
- Compounded risks introduces management complexities → maintaining cohesive care
- Healthcare access → gate-keeping at multiple levels

Prevention – requires access to integrated care models

- Regular education, screening and monitoring → early detection
- Lifestyle modifications → diet, exercise, cessation of smoking
- ART adherence → maintain immune function
- Mental health support and well-being

Patient is principal caregiver - has an active and informed role

- Majority of illness work takes place outside formal healthcare settings
- Emphasis on empowering self-management

HIV and NCD WHO 2021

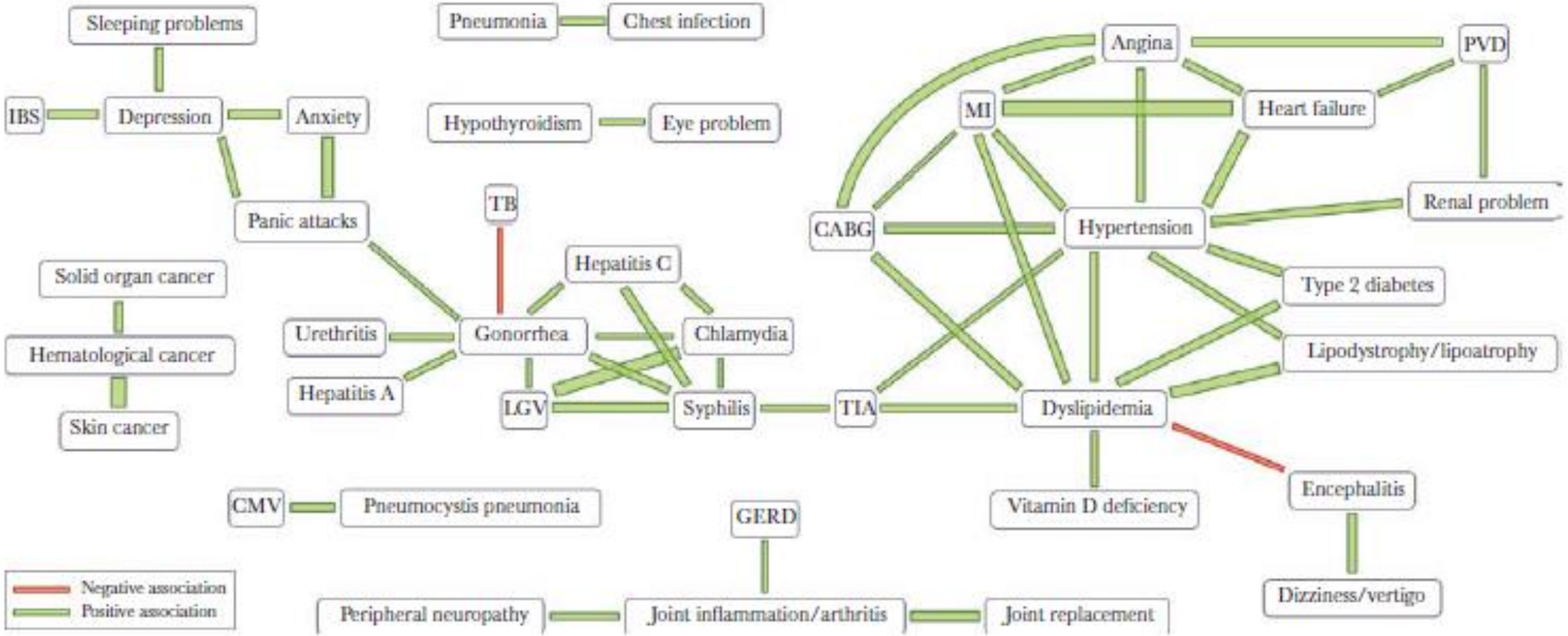


Figure 1. Significant nonrandom associations between comorbidities (as indicated by a significant Somers' *D* at the 0.1% significance level) in all POPPY PLWH (n = 1073). The thickness of the line is directly proportional to the absolute value of the Somers' D. Abbreviations: CABG, coronary artery bypass graft; CMV, cytomegalovirus; GERD, gastro-esophageal reflux disease; IBS, irritable bowel syndrome; LGV, lymphogranuloma venereum; MI, myocardial infarction; PLWH, people living with HIV; PVD, peripheral vascular disease; TB, tuberculosis; TIA, transient ischemic attack.

De Francesco et al, 2018; DOI: 10.1093/ofid/ofy272

Pregnancy and Lactation

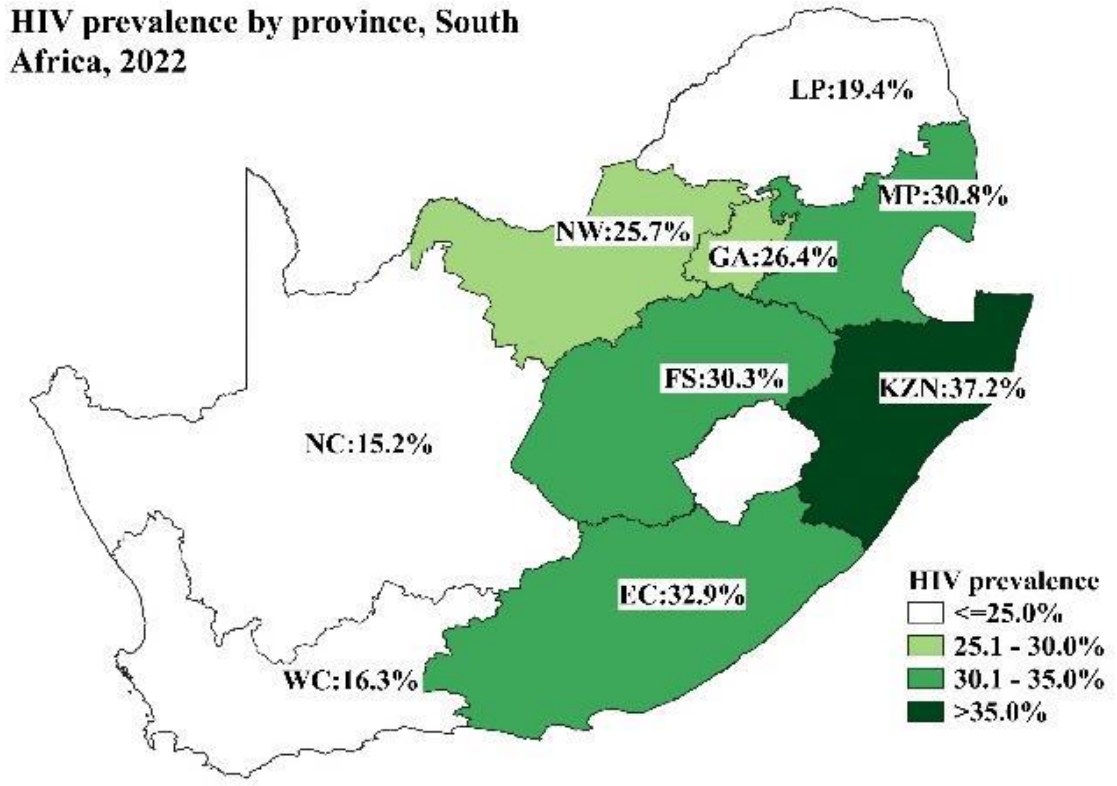
Special Considerations

Challenges

- Mother-baby pair as therapeutic unit – requires vigilance and support
  - Different physiology
  - Teratogenicity risk
    - Regimen adjustments may be necessary for certain opportunistic infections
- Limited evidence base
  - Trials tend to exclude pregnant women and infants
- Co-infections with the same transmission pathways
- Multiple healthcare contacts in a short period
- Globally 46% of all new HIV infections in 2022 were in young women and girls *(USAID 2022)*
  - South Africa - 48.1% of women who died in 2017 - 2019 triennium were PLWH

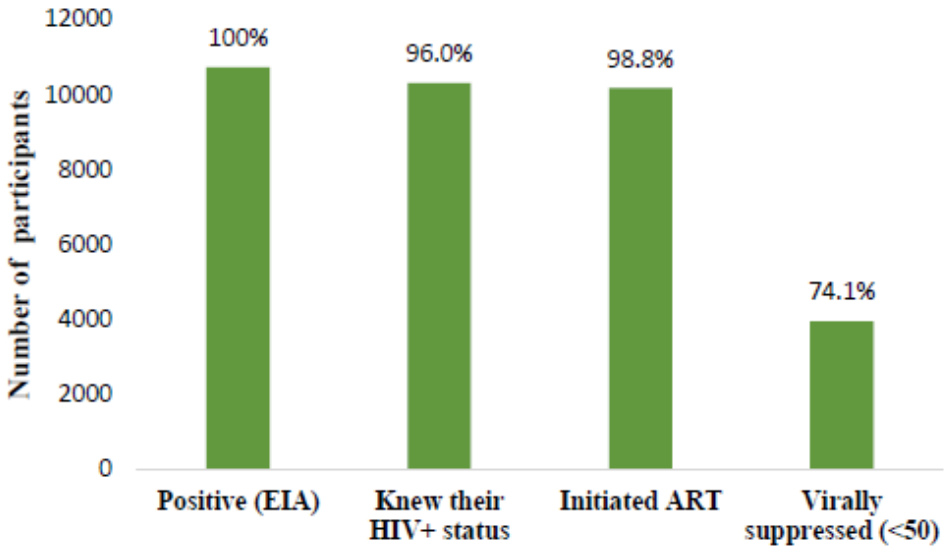
KEY CONSIDERATIONS

- Maternal health is central to healthy infant
- 4 pillars of PMTCT programmes
  - Primary prevention of HIV in WOCP
  - FP to prevent unintended pregnancies
  - Preventing vertical transmission through repeated HIV testing and ART
  - On-going care and support for women and their families
- VTP for syphilis, TB, hepatitis B, other STIs, malaria, listeriosis etc



Source: 2022 Antenatal HIV Sentinel Survey NICD

KEY CONSIDERATIONS



The denominator for each step is the size of the population in the previous step

Figure 17: HIV care cascade among antenatal women, in the 2022 HIV Antenatal Survey, South Africa

ART retention rates at 18mo post-partum about 63%

Successful VTP requires post-natal retention in care

Estimated Rate of MTCT HIV Without Any Intervention	
Timing	**Transmission Rate**
Overall: 40%	
In-utero	5-10%
Intra-partum	10-15%
Breast-feeding	5-20%
Overall, without breastfeeding: 15-25%	
Breast-feeding x 6mo	20-35%
Breastfeeding 18-24mo	30-35%

Acute HIV in Pregnancy

- Pregnancy and post-partum are high-risk for incident HIV
  - Biological factors (pregnancy)
  - Behavioral factors (pregnant woman and partner)
- Screen moms and know how HIV seroconversion presents
  - Pair antibody tests w/ HIV RNA
- Acute HIV = very ↑ risk for MTCT
  - ↑↑↑ VL in mom's plasma, genital tract, and breastmilk
  - No PMTCT ART as initially often undetected
  - Low levels of passively transferred maternal antibodies
- *MTCT rates up to 22% in HIV acquired during pregnancy vs 1.8% for HIV acquired before pregnancy
- Must retain HIV neg pregnant woman in care from first ANC visit until end of breast-feeding

*DOI: 10.1097/AOG.0b013e3181e00955

C-SECTION AS PMTCT?

- CS should be for obstetric indications
- Pre-ART era, CS complication rates HIV+ >> HIV - :urgent CS > elective CS > vaginal delivery
- Perinatal maternal VL most important predictor of MTCT
- Elective CS at term (38w0/7) for PMTCT before onset of labor and ROM regardless of ART (USA) if:
  - Maternal VL >1000 w/in 4w of delivery ***OR***
  - Unknown peripartum VL
- In moms w/ VL >1,000 copies/mL plus rupture of membranes
  - Risk of HIV transmission increases by 2%/h following rupture of membranes*
  - Require urgent delivery by safest means
    - Decision for operative delivery based on obstetric indications, not purely for PMTCT
  - MTCT risk very low if mom on ART and VL <1000

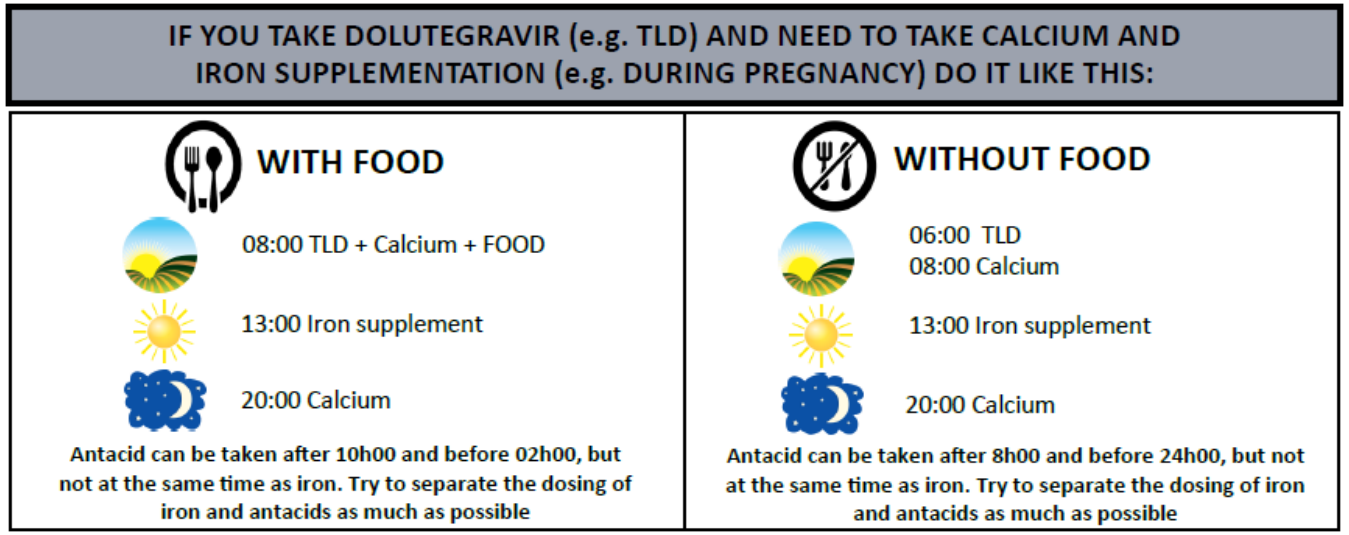
*http://pubmed.ncbi.nlm.nih.gov/11273216

PrEP in Pregnancy

- A key component of basic prevention packages → TDF/FTC
- Benefits outweigh potential harm
  - NB: Educate mom – PrEP does not prevent pregnancy or STIs
- Contra-indications: serum Cr >85umol
- Prescription intervals:
  - Initiation – neg HIV test, provide 1- month PrEP drug supply
  - 1 mo visit: repeat HIV test, if neg → 3-mo PrEP drug supply
  - q3 mo – repeat HIV test, if still neg → 3-mo PrEP drug supply
- Monitoring Cr baseline, 3 and 6 mo

ART Considerations

- Guideline ART regimens safe in all trimesters
  - *No excess risk for NTDs w/ DTG use
- TDF weight threshold 35kg→ 30kg
- ART switches → VL-dependent or VL-independent
- Use Cr ≥ 85µmol rather eGFR for TDF thresholds
  - 3TC adjustments → consult expert
- Regimens w/ TDF plus ATV/r require dose adjustment in 2nd and 3rd trimesters
  - ATV/r → 300/100mg to 400/100mg



Emesis during early pregnancy puts adherence at risk

Requires vigilance, screening and active management

**WHO, 2021, Tsepamo 2020*

SWITCHING EXISTING CLIENTS TO DTG-CONTAINING REGIMENS

Women who have already initiated ART on non-DTG containing regimens should be transitioned to a DTG-containing regimen as a matter of urgency. The table below provides guidance on non-VL dependent switching of existing clients to DTG-containing regimens.

NON VL-DEPENDENT REGIMEN SWITCHES
Regimens where the VL result will not influence nor delay the decision to switch to a DTG-containing regimen

Current Regimen	Criteria for switch	Regimen if change indicated
TEE ABC/3TC/EFV AZT/3TC/EFV AZT/3TC/DTG On any LPV/r or ATV/r regimen for less than 2 years duration	**Switch all to a DTG-containing regimen, regardless of VL result** Do VL at booking/1st ANC visit as for all pregnant women on ART. If VL at booking visit is not suppressed, continue to switch same day, but do ABCDE assessment and provide enhanced adherence counselling (EAC) if needed.	**TLD** provided no renal dysfunction and age > 10 yrs and weight > 30 kg If client does not qualify for TDF **ABC/3TC/DTG** If client does not qualify for TDF and has ABC hypersensitivity **AZT/3TC/DTG**

VL-dependent switches to DTG

Women who have been on PI-based regimens for more than two years also require a transition to a DTG-containing regimen. However, transitions in these women are VL-dependent: their VL result in the last 12 months will influence the decision of how and when to switch to a DTG-containing regimen. For further guidance, please refer to ***"Switching Existing Clients to DTG-containing Regimens" on page 15*** of the 2023 ART Clinical Guidelines

Source: Guideline for VTP of Communicable Diseases, NDOH 2023

TABLE 21: Timing of viral load monitoring during pregnancy, delivery and breastfeeding.

Period	ART initiation in pregnancy	Already on ART at diagnosis of pregnancy	Previously taken ART, not currently on treatment (ART interruption, ART for PMTCT)	Newly diagnosed HIV infection during delivery or breastfeeding
Antenatal	VL at baseline and after 3 months of ART: if > 28 weeks' gestation, then repeat VL at delivery	VL at first ANC visit	VL at initiation of DTG-based regimen; repeat VL 3 months later (change in VL determines management)	-
Delivery	All women need VL measurement at delivery; review result at day 3–6 postnatal visit			-
Postnatal, up to the end of breastfeeding	At 6 months postpartum, then VL 6-monthly until 6 weeks after cessation of breastfeeding			VL after 3 months on ART, then 6-monthly during breastfeeding until 6 weeks after cessation of breastfeeding

ANC, antenatal care; ART, antiretroviral therapy; DTG, dolutegravir; VTP, vertical transmission prevention; VL, viral load.

- ❑ Use appropriate VTP codes to get timely VL results and prevent EGK
- ❑ VL threshold for action is >50cpml – results must be checked w/in 1 week
- ❑ ABCDE approach for unsuppressed VL, repeat VL in 4-6w
- ❑ Consider resistance testing and prompt ART regimen switch in:

TLD ≥2y plus ≥2 consecutive VL ≥1000 taken ≥2y on TLD plus adherence >80%

Making Breastfeeding Safer

- Exclusive BF for 1st 6mo
  - Continue BF x ≥2y
  - Introduction of nutritionally adequate, appropriate and safe complementary feeding at 6mo
- Full adherence to ART – all current guideline regimens safe in breasfeeding
- ART still reduces risk of postnatal transmission in the context of mixed feeding.
  - BF x <12 months better than never initiating breast-feeding
  - Prioritise donor human milk when a supplement is required
- HIV neg moms → HIV risk reduction, regular HTS, infant feeding support
- HIV pos moms → lifelong ART, infant prophylaxis, infant testing, HIV risk reduction, infant feeding support

Won't Breastfeed, Can't Breastfeed

- Indications
  - Mother's choice
  - Mother demised
  - Mother incapable of caring for infant
  - Infant abandoned
  - Medical conditions in mother or baby

- Avoid abrupt cessation of BF +/- followed by intermittent BF → increases transmission risk

- Mom on 2nd and 3rd line ART w/ unsuppressed VL
  - Intensive formula feeding support and monitoring via therapeutic nutrition programmes

- Appropriate counselling on safe management of formula

- Pasteurised full cream milk from age 12y

- Continue infant ART prophylaxis until 4w post-cessation of BF

THANK YOU