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Preparing for Third Line Agents

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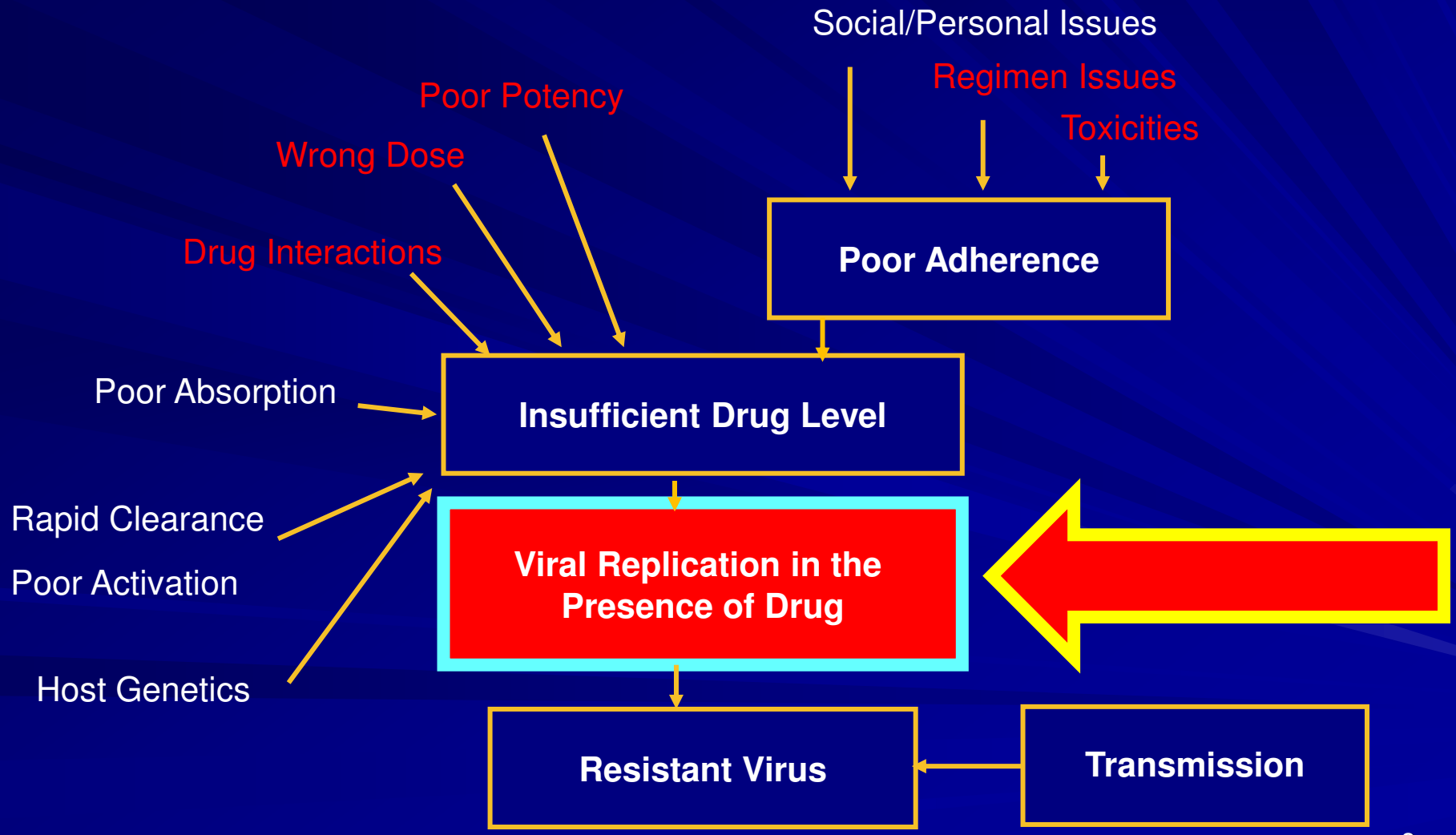
Overview

- Factors contribute to resistance
- Pathogenesis of resistance
- Definition of treatment failure
- Critical facts - genotyping
- Genetic barriers to resistance
- Local data
- Review of third line agents
- DOH Process

Factors that contribute to the Development of Resistance

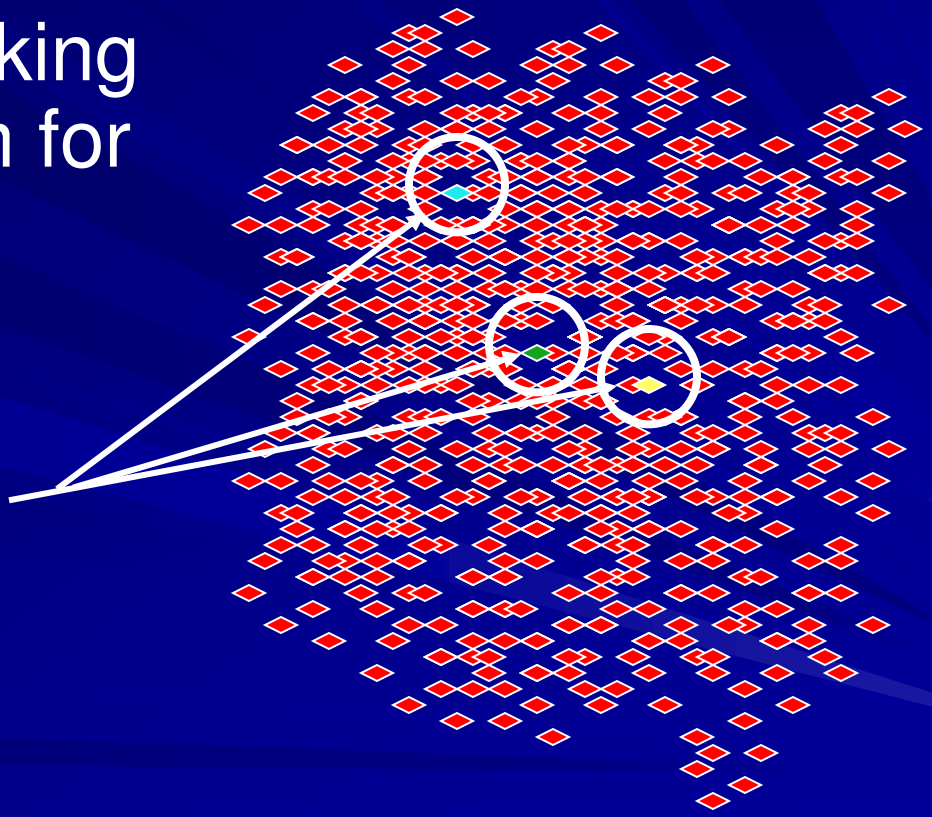


Pathogenesis of Ω

- Error prone RT enzyme
- Mistakes ⇒ mutant forms of the virus
- Mutations ⇒ occur randomly in the genome altering structural proteins, regulatory proteins or enzymes.

Growth in the absence of inhibitory pressure

- HIV multiplies freely taking the most optimum form for rapid growth $\rightarrow$ wt.



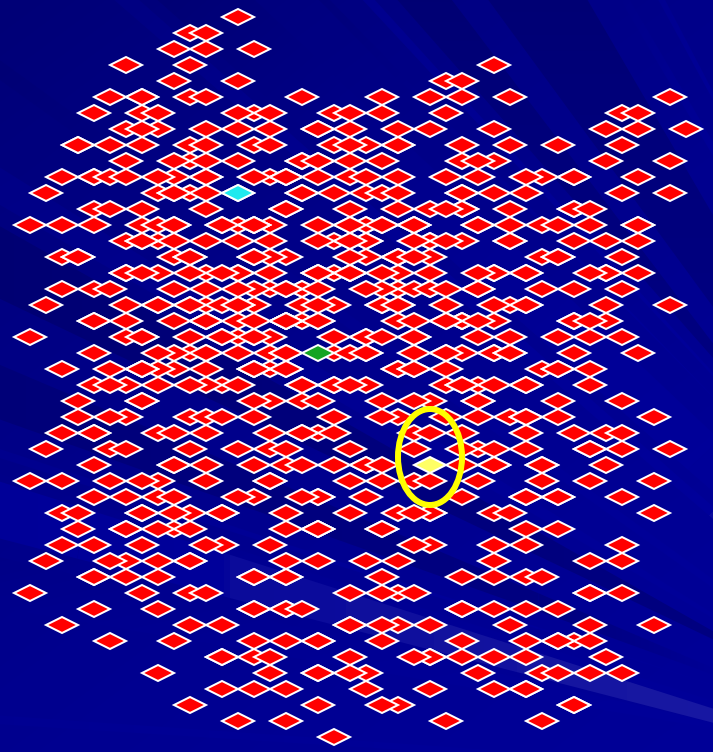
- As it proliferates $\Rightarrow$ spontaneous random mutations

Growth in the presence of ARV pressure

- ARVs kill all of the original wild type organisms

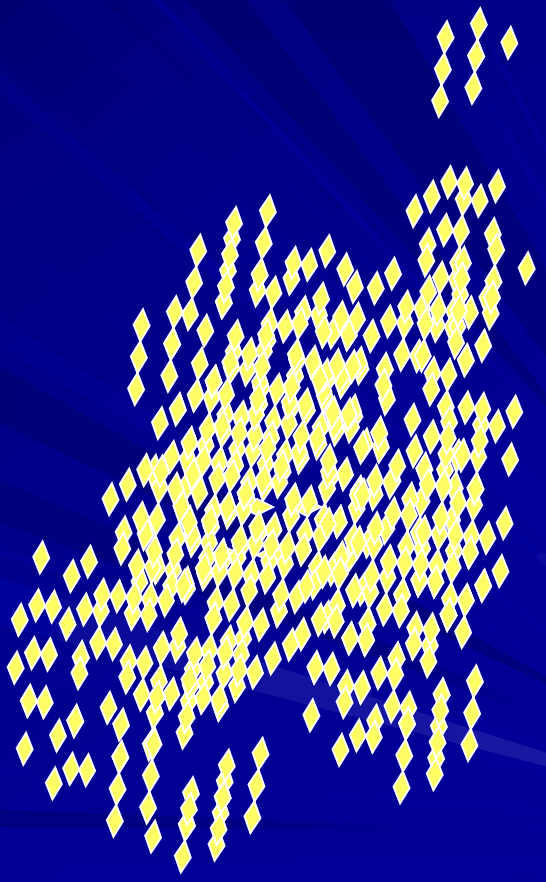
but

- The mutated virus which is RESISTANT survives.

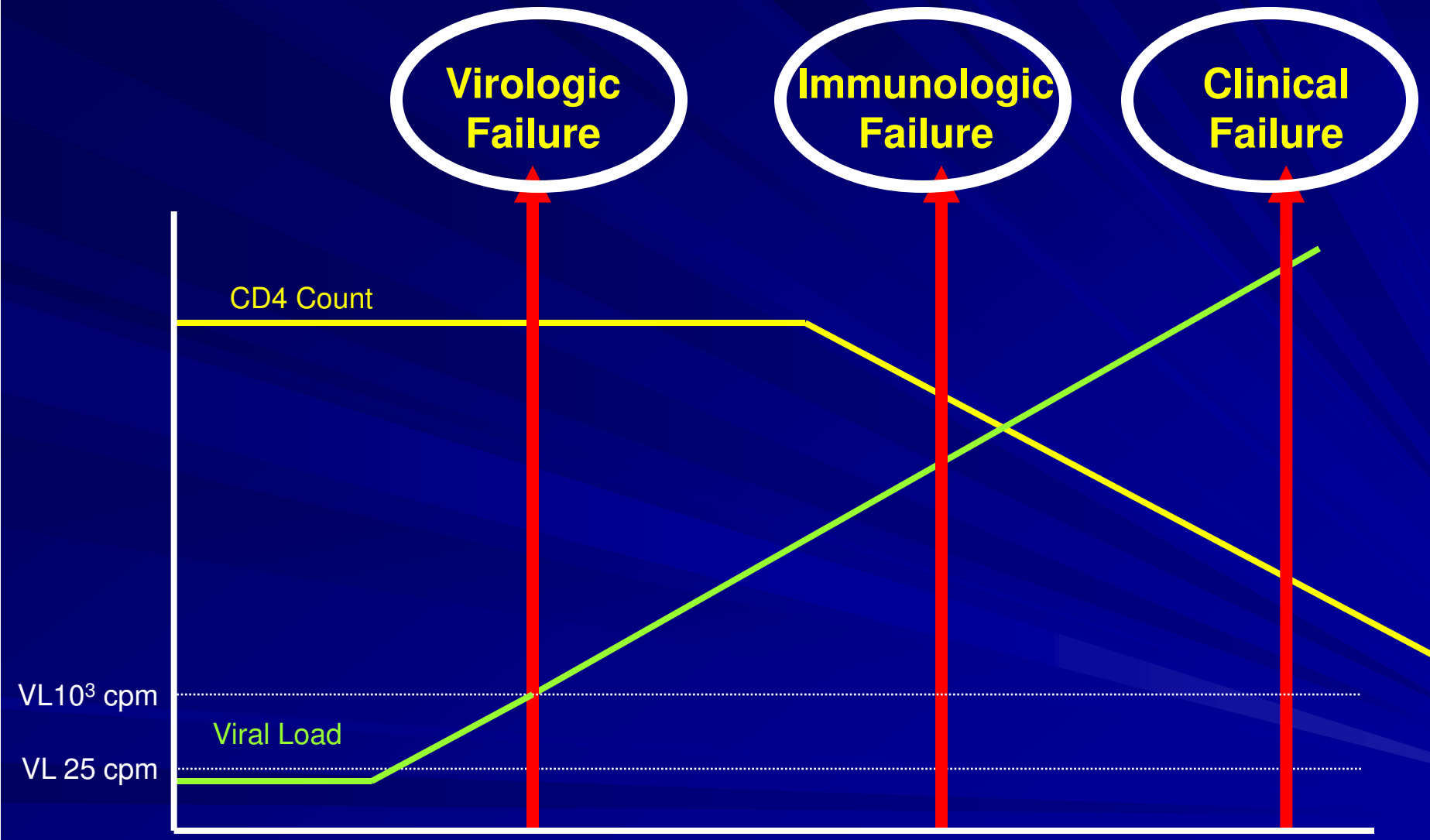


Growth in the presence of ARV pressure

- Mutated HIV grows & multiplies, even in the presence of ARVs.
- This virus is now RESISTANT & will continue to replicate albeit at a slower rate due to reduced fitness.
- Note resistant virus are “archived” in long lived cells - may fade but not disappear when drug stopped.

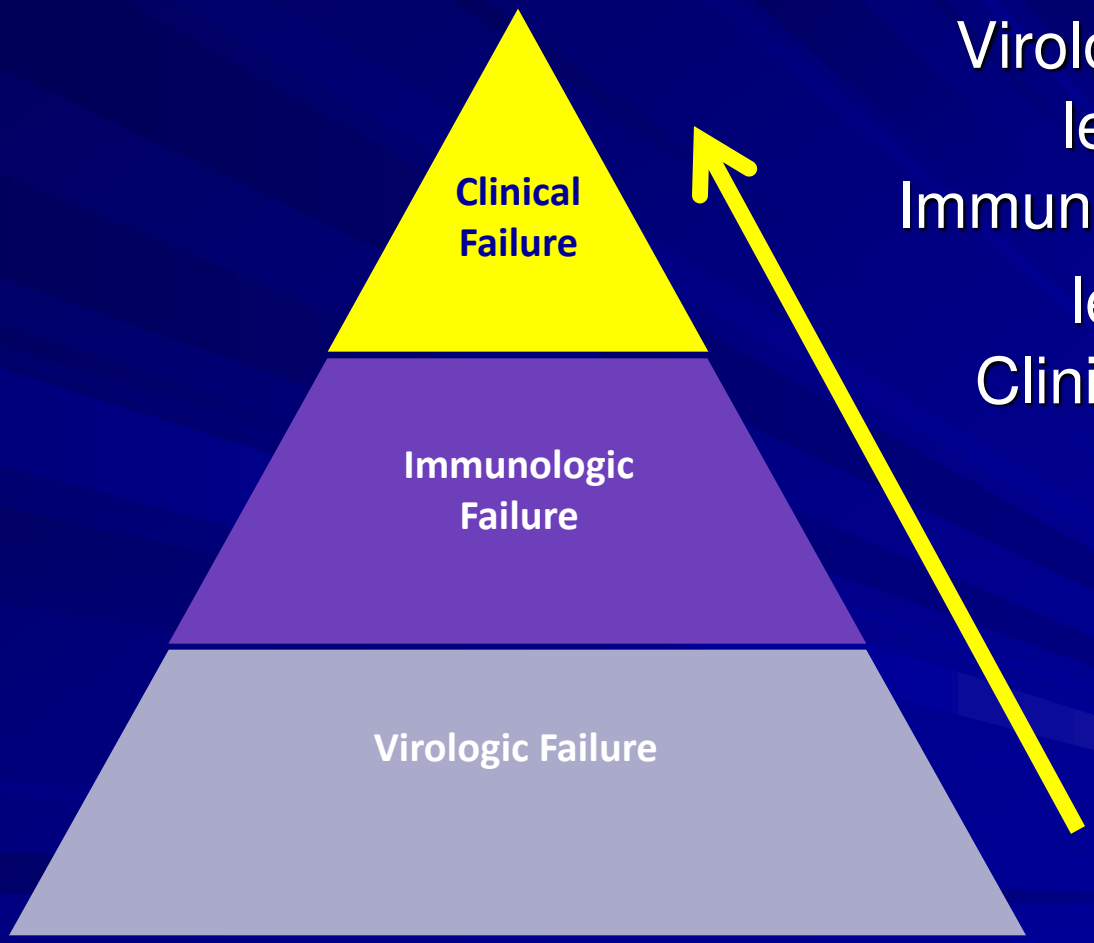


Treatment Failure VL - Early & Sensitive



Murri R, *et al. JAIDS*. 2006;41:23-30.
Losina E *et al, 15th CROI* 2008, #823
Pillay D, *et al. 14th CROI*, Los Angeles 2007, #642

Clinical Failure is Just the Tip of the Iceberg



Virologic failure leads to Immunologic failure leads to Clinical failure

Murri R, *et al. JAIDS*. 2006;41:23-30.
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Definition of Virologic failure

2 consecutive viral loads >1000cpm after adequate exposure to ART

Facts on resistance testing

- Minimum VL required 1000 cpm
- Measures dominant HIV strains (>20%)
- Does not detect virus in sanctuary sites
- Does not detect mutant “archived” viruses selected by past treatment
- Important to obtain comprehensive past drug history & outcome of past regimens
- Most reliable for detecting Ω to current or recently discontinued

To Decide on a Third Line Regimen

Need to know all ARVs patient has experienced in the past

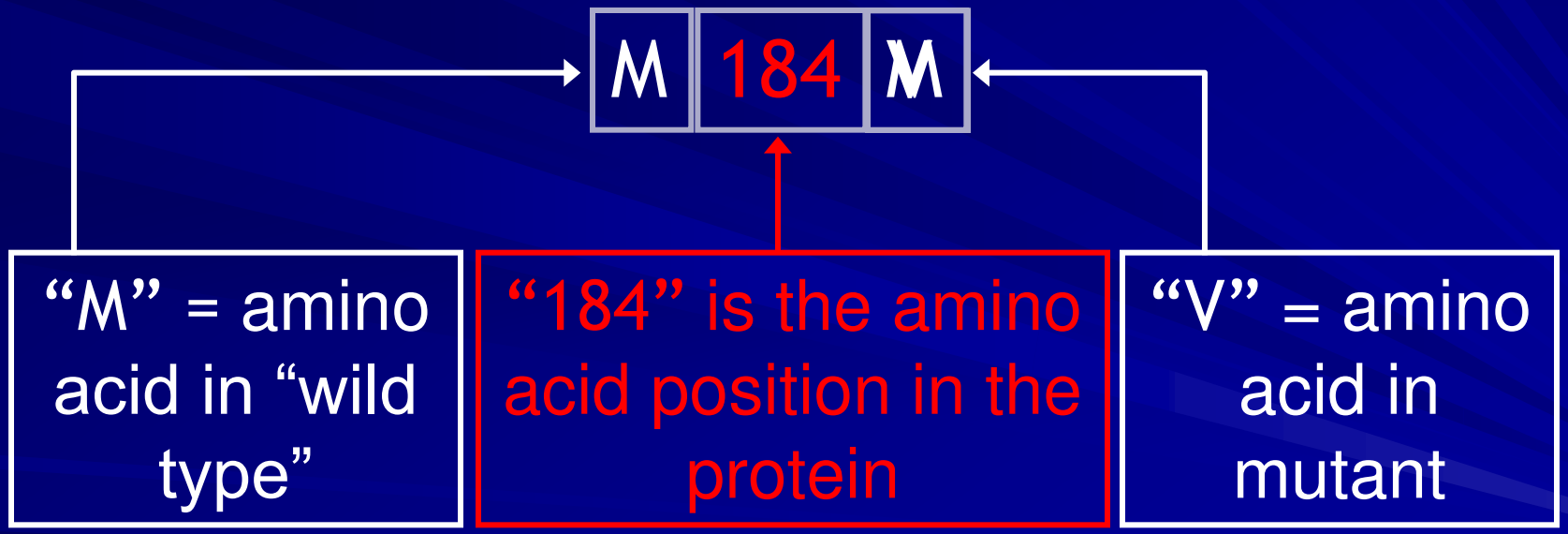
Need to know reasons for discontinuation

Need to know regimen patient is on at time of resistance testing

Resistance testing must be done when the patient is on the failing regimen

Designation of Mutations

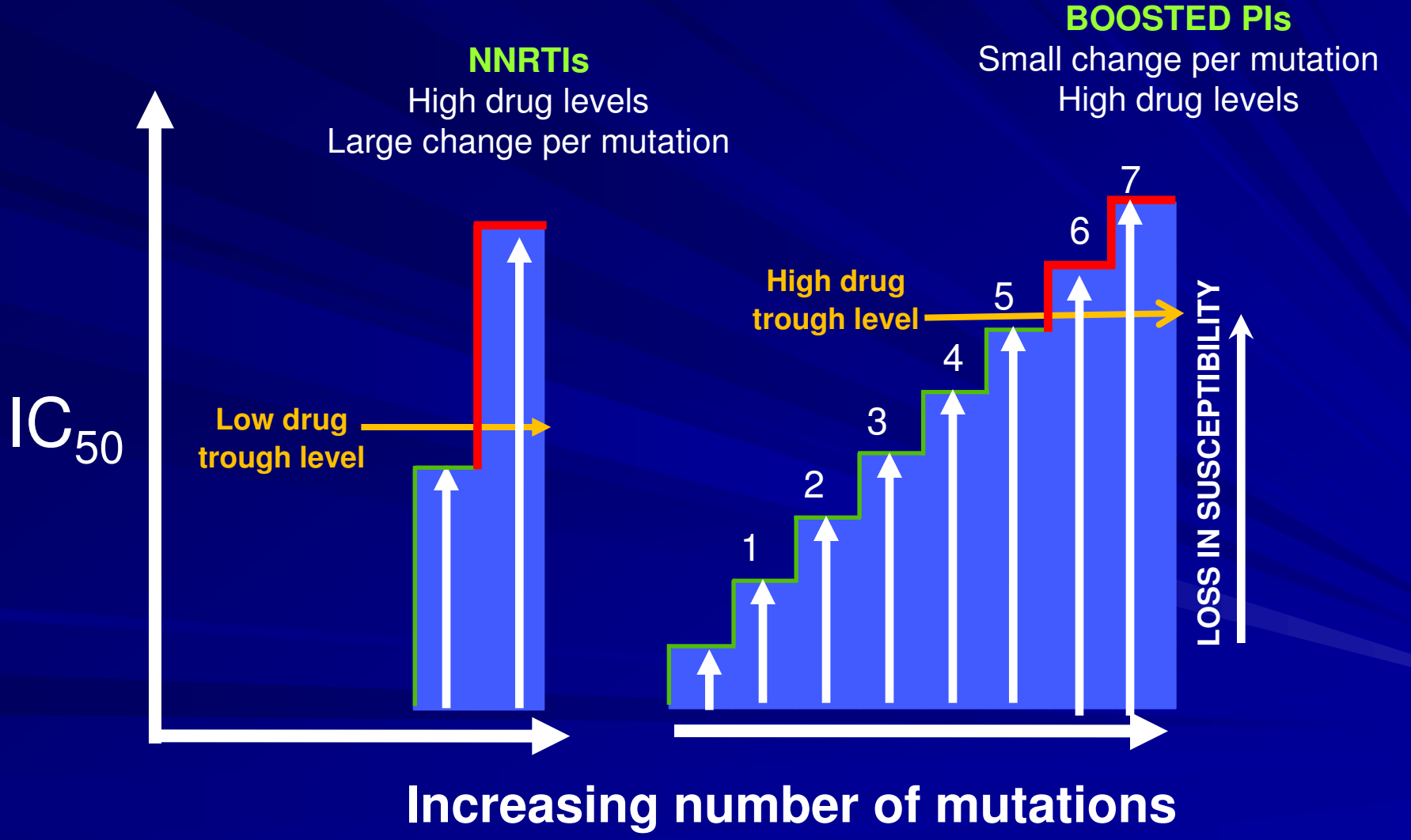
- How do we identify a resistance mutation?



Important Property of ARVs - Genetic Barrier to Ω

- Number of mutational steps the virus must undergo for clinically significant drug resistance
- High genetic barrier means the virus needs to undergo many mutations to become resistant.

Pharmacokinetic & Genetic Barriers to Resistance



Brun S *et al., 8th ECCATH*, Athens, October 2001, #7

Genetic Barrier of Drug Classes

DRUG CLASS	GB
Unboosted PI	1
NNRTI	1
NRTI	1/2/3 *
Fusion Inhibitor	1
Boosted PI	3–8

***Up to 3 for thymidine analog mutations**

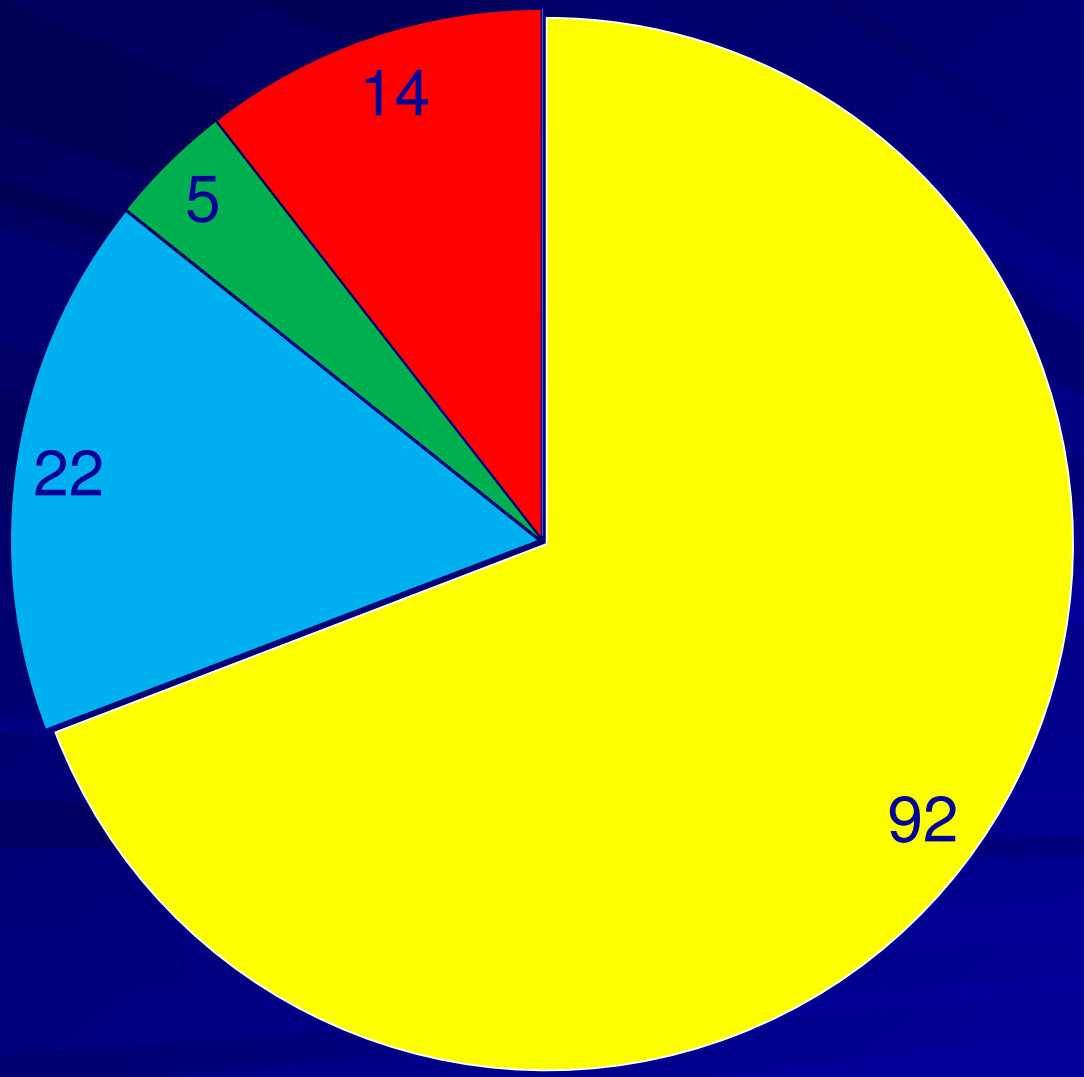
http:// www.hivfrenchresistance.org/2006/tab2.html *General estimation of approved drugs, Nov 2006

Local Study

- Second line treatment for ≥ 6/12
- Clinician convinced patient adherent:
  - Direct questions
  - Pill counts
  - Clinic attendance
  - Adherence to script refills

Study PI: Dr. M. Gordan

Mutations Requiring Third line Agents



N=144

- No Significant PI pressure
- Triple Class
- PI + NRTI

27/119 = 23%

Message from Study

- Most drug failures occur without significant mutations $\Rightarrow$ non-adherence
- Resistance testing is effective but expensive means to determine adherence
- Cost benefit favors resistance testing

HIVDR Early Warning Indicators (EWI)

- Pharmacy refill
- Clinic visits
- Pill counts – self reported adherence
- Clinical risk factors
- Psychosocial risk factors

*WHO recommends (http://www.who.int/hiv/topics/drugresistance/indicators/en/index.html)

Drugs for Third-line

- Lamivudine
- Tenofovir
- Raltegravir
- Boosted Darunavir
- Etravirine

Why recycle 3TC

- Well tolerated - no mito toxicity
- Low pill burden
- M184V decreases viral fitness
- Antagonizes development of TAMs, K65R, and Q151M.
- Enhances activity again AZT, d4T, TDF resistant virus

Raltegravir- Integrase Inhibitor

- Dose is 400 mg bd. With or without food
- Metabolized by glucuronidation
- No dose adjustment in hepatic or renal impairment. No data in severe disease.
- RAL does **not** use, induce or inhibit CYP
- Significant interaction with rifampicin 40% reduction in AUC →↑ to 800mg bid
- Overall, raltegravir was well tolerated - N, V, D, fatigue, H/A, increased CPK ? significance.

Etravirine

- 200mg bid with food.
- No dosage adjustment in renal disease.
- No dosage adjustment mild/moderate liver disease.
- N, V, D, abd pain, rash^
- Hepatotoxicity- HBV/HCV
- Lipid abnormalities
- Pregnancy Category B drug

Etravirine

- Active against NVP & EFV resistant virus
- Ω depends on no. & type of mutations
- Prevent accumulation of NNRTI mutation.
- Drug interactions
  - Substrate & inducer of CYP.
  - No dose adjustment DRV/r, RAL, TDF.
  - Do not use with RIF.

Darunavir

- Darunavir - potent PI activity vs. MDR
- Always boosted with RTV (14x↑)
- Bioavailability ↑ed ~30% with food
- Rx experienced DRV/r 600/100 bd
- Rx naïve DRV/r 800/100 mg OD
- Is SA recommended in Rx-experienced

Darunavir

- Metabolized by the CYP3A4
- Mild to moderate liver disease no dosage adjustment , C/I in severe hepatic
- No does adjustment in RF
- Toxicity:
  - Hepatotoxicity- 0.5%
  - Rash- 7%
  - Glucose intolerance, lipodystrophy
  - GI intolerance- N, V, D, abd pain
  - Headache

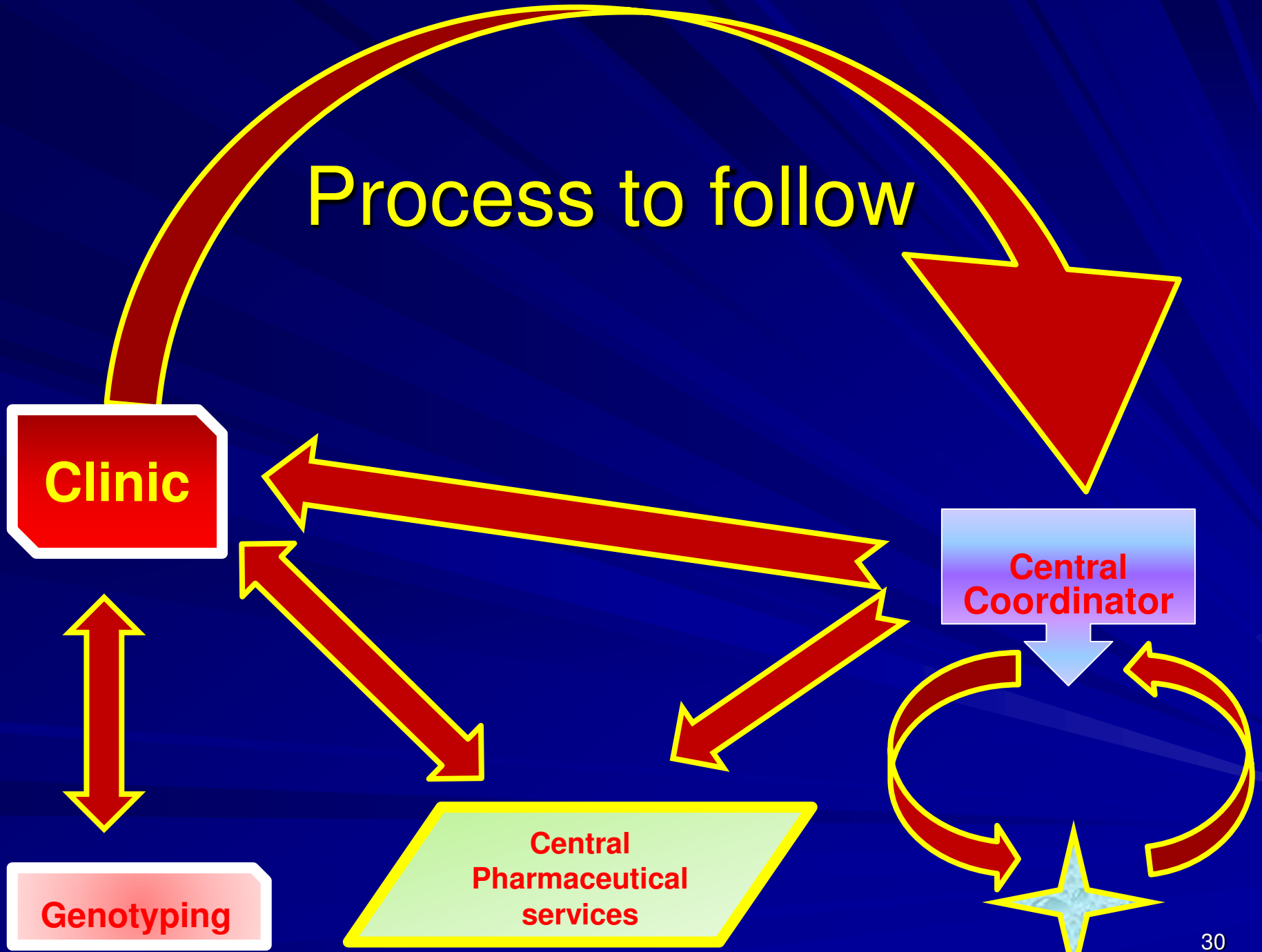
Activity against PI Resistant Strains

- High genetic barrier to resistance
  - ≥3 DRAMS on background of ⇒14 PI RAMS
- Factors associated with hi risk of DRAMs
  - No. of PI experienced in past
  - Duration on a failing PI

Principals Providing Third line Agents

- Decentralize - allow wide accessibility
- Doctor/ ± nurses:
  - know the drugs, drug interactions/toxicity
  - ensure adherence, regular attendance,
  - Treat “special” - maintain control, Pt. education,
- Pharmacist:
  - monitor, evaluate,
  - Supply chain/storage/accountability
  - Patient education
  - Active patient follow-up

Process to follow



Motivation Forms

- Patients details
- Facility details
- Past ART - drugs/duration/ why discontinued
- Concomitant medication
- Serial recent CD_4/VL/ Safety bloods (ALT, Cr, WCC)
- Genotype

Contact Numbers

- Department of Virology: Registrar
  - 031 240 2599
  - 031 240 6000
  - 031 240 2794

- The Secretariat: jamalk@health.gov.za

Conclusion

- Third line agents are here
- Adherence - cause of failure
- Critical to detect resistance early for optimum effect of third-line agents.
- Genotypic analysis has limitations
- Consider drug interactions of third line agents.
- Engage third line process responsibly
- Use third line agents prudently

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