Southern African HIV Clinicians Society

3rd Biennial Conference

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Sandton Convention Centre
Johannesburg

Our Issues, Our Drugs, Our Patients

www.sahivsoc.org
www.sahivsoc2016.co.za

Prevention is better than cure

TRANSMITTED RESISTANCE, TESTING, PITFALLS, ADHERENCE

Case

- 38-year-old female from Johannesburg.
- HIV positive.
- Initiated on FTC/TDF/EFV in August 2015.
  - Along with Vitamin B co and TMP/SMX (Bactrim).
- CD4 at baseline was 4 cells/µL.
- Baseline viral load was 66 983 copies/mL.

Case

- Reported no problems at one month visit, but came into the clinic one month later to report troubling watery diarrhoea, ever since starting the ARVs.
  - At least 8 times per day.
  - No blood or pus.
  - Had lost roughly 4 kg since then: 48 to 44 kg.
- Loperamide added. Stool MCS, ova and parasites sent off:
  - No growth, no parasites or ova observed.

Question

- In this patient, what is the most likely diagnosis?
  A. (Cyst)isospora belli diarrhoea
  B. Cryptosporidium diarrhoea
  C. ARV-induced diarrhoea
  D. Shigella diarrhoea

Answer

- **Cryptosporidium diarrhoea**
- Isosporiasis is unlikely since the patient is on TMP/SMX (Bactrim) prophylaxis.
- Shigella diarrhoea is typically a short-lived (days) dystentery (blood and/or pus), and will usually culture on stool MCS.
- ARV-induced diarrhoea is uncommon with FTC/TDF/EFV, and is seldom so severe as to cause weight loss.

Management

- As per DOH Standard Treatment Guidelines for chronic diarrhoea in an HIV-positive adult:
- Send off stool for MCS, ova & parasites.
  - If stool is negative or shows cryptosporidium, give **loperamide** and commence ART.
  - If stool is positive for *Isospora belli*, give **Cotrimoxazole** and commence ART.

The patient was given loperamide and told to return in 1 month's time. TB blood culture (Bactec) was pulled also, due to consideration of possible MAC infection.

Maximising stool ova/parasite yield

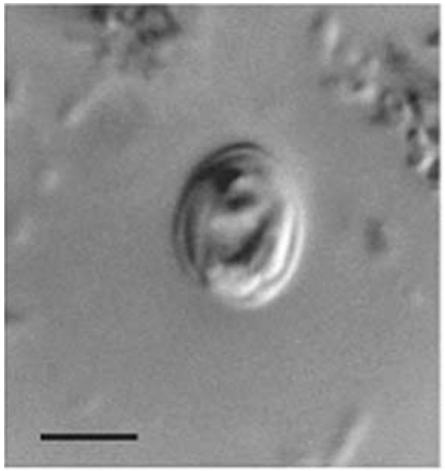
- Unlike bacterial causes of diarrhoea (e.g. pathogenic E. coli, non-typhoidal salmonella, Shigella, etc.), most parasitic ova and oocysts are shed intermittently.
  - Therefore, sending more than one stool sample can increase yield. Best strategy seems to be 3 samples on consecutive days.
- Oocysts and ova degrade with time – if possible, ensure a fresh sample is viewed by the lab within 4 hours.

Further history

- At the next month's visit, the patient still complained of diarrhoea, and had lost another 2 kgs.
  - A 2nd stool specimen was also negative for MCS, ova and parasites.
- A few weeks later the patient returned again, still complaining of diarrhoea.
- A 3rd stool specimen showed **cryptosporidium oocysts** on microscopy.

Cryptosporidium

- Protozoan.
- Causes voluminous watery diarrhoea.
- Anyone can get it, but it's self-limiting (5-10 days) in hosts with normal immunity.
- HIV patients:
  - CD4 > 150: self-limited
  - CD4 < 100: chronic
  - CD4 < 50: fulminant



Cryptosporidium

- No effective treatment.
- Best bet is to give loperamide and try to get the CD4 up as quickly as possible with ART.

Further management

- A viral load was done at 4 months. It had gone from 67 000 to 83 000 copies/µL.
- Patient claimed 100% adherence. Was sent for readherence counselling.
- 2 months later, her diarrhoea and weight loss had become so severe that she was admitted to hospital.
- Her viral load was now 133 000 copies/µL. Her stool showed cryptosporidium again (and was negative for *C. diff*).

Summary

- 38-year-old female with chronic cryptosporidium diarrhoea, complicated by significant weight loss (48 → 37 kg in 5 months) and now dehydration.
- Failing ART therapy:
  - Viral load had gone from 67,000 at baseline to 87,000 at 4 months, to 133,000 at 6 months.
  - CD4 had gone from 4 to 32 over the same period.

Why is the patient failing ART?

- Adherence
- Resistance
- Pharmacokinetics

Adherence?

- Patient swore 100% adherence.
- Knew the names and doses, and had a cellphone reminder set to help her take her pills on time.
- Stated that she understood that only her ART would “cure” her cryptosporidium.
- Said that her weight loss and profuse diarrhoea was causing her job to become threatened.
- Was in tears that “no one believed” her that she was taking her medication.

Why is the patient failing ART?

- Adherence
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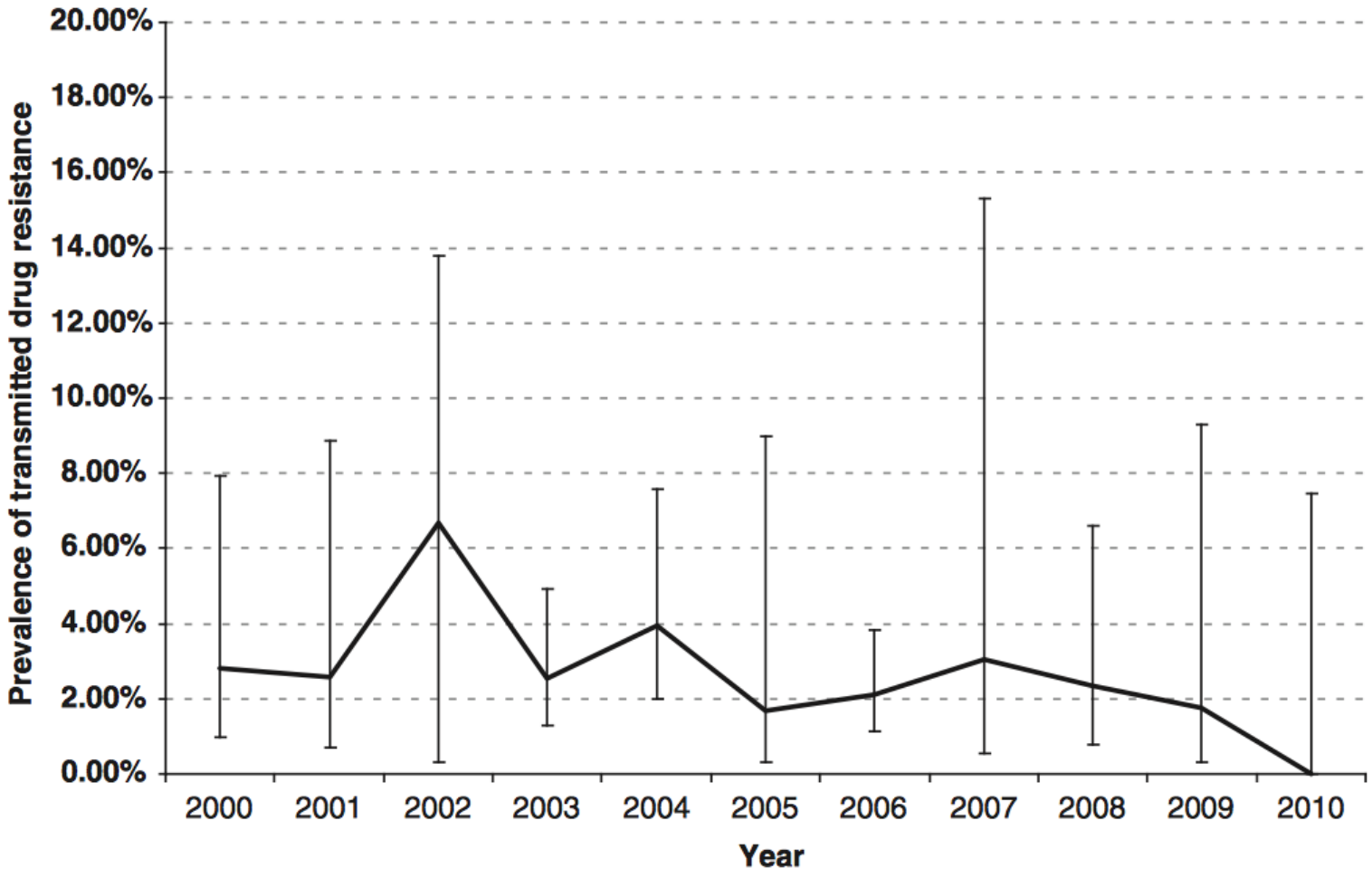
Resistance?

- A patient who is near 100% adherent shouldn't fail her therapy so soon…
- Unless there's transmitted resistance.

Primary Drug Resistance in South Africa: Data from 10 Years of Surveys

Justen Manasa,[1] David Katzenstein,[2] Sharon Cassol,[3] Marie-Louise Newell,[1] and Tulio de Oliveira,[1] for the Southern Africa Treatment and Resistance Network (SATuRN)

AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 28, Number 6, 2012



NATIONAL SURVEILLANCE OF TRANSMITTED HIV-1 DRUG RESISTANCE IN 2012

Gillian Hunt[1], Johanna Ledwaba[1], Monalisa Kalimashe[1], Anna Salimo[1], Siyabonga Cibane[1], Beverly Singh[1], Adrian Puren[1], Simbarashe Takuva[1], Natalie Exner Dean[2], Michael R. Jordan[3] & Lynn Morris[1]

- Analysis of specimens collected as part of the 2012 National Antenatal HIV/HSV-2 Prevalence Survey.
    - Primigravid women < 21 years
    - Anyone with detectable ARVs (AZT, EFV, FTC, LPV, NVP, TDF) were excluded.

Province	Number of specimens amplifiable by genotyping PCR	Genotyping amplification rate	Number of sequences with PI mutations	PI Point Prevalence (95% CI)	Number of sequences with NRTI mutations	NRTI Point Prevalence (95% CI)	Number of sequences with NNRTI mutations	NNRTI Point Prevalence
Eastern Cape	99	88.4%	0	0% (0 - 3.7)	0	0% (0 - 3.7)	3	3% (1.0 - 8.5)
Free State	54	76.1%	0	0% (0 - 6.6)	1	1.9% (0.3 - 9.8)	4	7.4% (2.9 - 17.6)
Gauteng	65	69.1%	1	1.5% (0.3 - 8.2)	0	0% (0 - 5.6)	6	9.2% (4.3 - 18.7)
KwaZulu-Natal	196	64.5%	0	0% (0 - 1.9)	4	2% (0.8 - 5.1)	8	4.1% (2.1 - 7.8)
Limpopo	20	47.6%	0	0% (0 - 16.1)	0	0% (0 - 16.1)	2	10% (2.8 - 30.1)
Mpumalanga	45	76.3%	0	0% (0 - 7.9)	1	2.2% (0.4 - 11.6)	2	4.4% (1.2 - 14.8)
North West	21	44.7%	2	9.5% (2.7 - 28.9)	0	0% (0 - 15.5)	1	4.8% (0.8 - 22.7)
Northern Cape	4	57.1%	0	0% (0 - 49.0)	0	0% (0 - 49.0)	0	0% (0 - 49.0)
Western Cape	28	82.4%	0	0% (0 - 12.1)	0	0% (0 - 12.1)	2	7.1% (2.0 - 22.6)
National	532	69.1%	3	0.6% (0.1 - 1.6)	6	1.1% (0.5 - 2.4)	28	5.3% (3.7 - 7.5)

Transmitted resistance in SA

Province	Number of specimens amplifiable by genotyping PCR	Genotyping amplification rate	Number of sequences with PI mutations	PI Point Prevalence (95% CI)	Number of sequences with NRTI mutations	NRTI Point Prevalence (95% CI)	Number of sequences with NNRTI mutations	NNRTI Point Prevalence
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Transmitted resistance

- MUCH more likely to get one of the signature NNRTI mutations transmitted than those of other classes.
  - These strains don't affect the viral fitness much, and so the wild type virus (with no mutations) can't outcompete them.
  - This means that the strains present in the person who transmits the virus will often contain viral strains with mutations like K103N, even if they're no longer taking their ART, or are taking a non-NNRTI-based regimen.

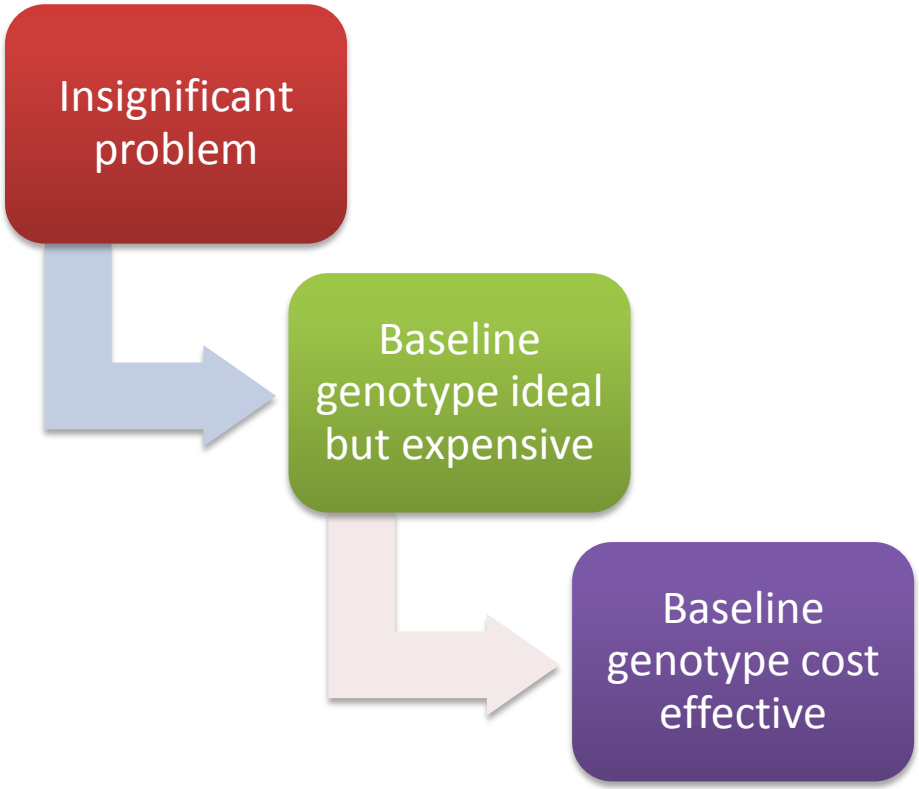
Not at all unique

- WHO:
  - <5% transmitted resistance = low
  - 5-15% = moderate
  - > 15% = high
- USA (2012):
  - 15.2% TDR overall
  - ≈ 2.5% TDR to 2 drug classes
  - ≈ 0.6% TDR to 3 drug classes

One solution

- In the USA, for instance, a **baseline genotype** is recommended before treatment initiation to assess for transmitted drug resistance.

As TDR to 1st line drugs increases…



South African costs

- In State Sector, 2015 price of HIV drug resistance testing was recently decreased to R1797.68 per assay.
- Doing a baseline genotype on the remaining 3 million people who are yet to start ART would cost over **R5 billion**.

South Africa

- Current surveys underway seem to be pointing to increasing TDR, especially to NNRTIs.
- This is to be expected.
- Long term course will depend on:
  - Whether 1st line contains a NNRTI
  - How well the health system functions
  - Cost-effectiveness of baseline genotyping

Why is the patient failing ART?

- Adherence
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Effect of diarrhoea on ART absorption

- Probably minimal effect:
  - 2 small studies from 1990s on AZT pharmacokinetics in HIV-infected patients with chronic diarrhoea

Impaired absorption of zidovudine in patients with AIDS-related small intestinal disease.

Kapembwa, Moses S.; Fleming, Simon C.; Orr, Malcolm; Wells, Carol; Bland, Martin; Back, David; Griffin, George E.

AIDS:
November 1996

- Reduced Cmax and delated Tmax (i.e. delayed absorption) but no change in AUC.

Zidovudine absorption and small intestinal function in HIV seropositive patients

K. Allan Macnab[a], M. J. Gill[b,c,e], L. R. Sutherland[b,c], A. Murphy[c] and R. Brant[d]

Journal of Antimicrobial Chemotherapy (1996) **37**, 825–829

Table. Non-compartmental kinetic parameters after 200 mg zidovudine

Parameter	Diarrhoea $n = 15$	No diarrhoea $n = 20$	Confidence intervals
AUC (mg/L.h)	1.13 S.D. 0.30	1.07 S.D. 0.36	−0.17 to 0.29
$T_{\frac{1}{2}}$ (h)	0.97 S.D. 0.21	1.00 S.D. 0.27	−0.2 to 0.14
T_{max} (h)	0.67 S.D. 0.25	0.72 S.D. 0.28	−0.24 to 0.13
C_{max} (mg/L)	1.03 S.D. 0.33	1.14 S.D. 0.50	−0.41 to 0.19
CD4 counts/mm^3	135 S.D. 169	169 S.D. 168	

[a]No significant differences seen for any parameter.

AIDS-Associated Diarrhea and Wasting in Northeast Brazil is Associated With Subtherapeutic Plasma Levels of Antiretroviral Medications and With Both Bovine and Human Subtypes of *Cryptosporidium parvum*

The Brazilian Journal of Infectious Diseases 2003;7(1):16-22

- Observational trial of 12 patients with diarrhoea admitted to hospital in Brazil, showing an ***association*** between chronic diarrhoea (*Cryptosporidium* and *Isospora* mostly) and lower drug levels.
- **Massive** problem of confounders – barely addressed in the study.

AIDS Diarrhea and Antiretroviral Drug Concentrations: A Matched-Pair Cohort Study in Port au Prince, Haiti

Am. J. Trop. Med. Hyg., 84(6), 2011, pp. 878–882

- 26 patients in each arm
- No differences in plasma levels of either 3TC/AZT or EFV at 2 or 4 weeks.
- No differences in viral load at 24 weeks.

Why is the patient failing ART?

- Adherence
- Resistance
- Pharmacokinetics

Management options

A. Change to 2nd line ART
   - Patient has technically failed 1st line: 2 viral loads > 1000 copies/mL, 2 months apart despite counselling.

B. Persist with 1st line ART but do further adherence counselling.
   - Patient is extremely unlikely to have failed first line so quickly if her compliance had been adequate.

C. Another option?

Academic tertiary hospital

Genotype

Drug Resistance Interpretation: PR	
PI Major resistance mutations	None
PI Minor resistance mutations	None
Protease Inhibitors:	
Atazanavir/r (ATV/r)	Susceptible
Darunavir/r (DRV/r)	Susceptible
Fosamprenavir/r (FPV/r)	Susceptible
Indinavir/r (IDV/r)	Susceptible
Lopinavir/r (LPV/r)	Susceptible
Nelfinavir/r (NFV)	Susceptible
Saquinavir/r (SQV/r)	Susceptible
Tipranavir/r (TPV/r)	Susceptible

Genotype

Drug Resistance Interpretation: RT				
NRTI resistance mutations	K65R A62V/A	M184V	Y115F	
NNRTI resistance mutations	G190A	K101E	V106M	Y181C
	Nucleoside RTI:			
Lamivudine (3TC)	High-level resistance			
Abacavir (ABC)	High-level resistance			
Zidovudine (AZT)	Susceptible			
Stavudine (D4T)	Intermediate resistance			
Didanosine (DDI)	High-level resistance			
Emtricitabine (FTC)	High-level resistance			
Tenofovir (TDF)	High-level resistance			
	Non-Nucleoside RTI:			
Efavirenz (EFV)	High-level resistance			
Etravirine (ETR)	High-level resistance			
Nevirapine (NVP)	High-level resistance			
Rilpivirine (RPV)	High-level resistance			

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