HIV Drug Resistance South Africa, How to address the increasing need?

14 Apr. 2016

Thus the HIV DR needs to focus on prevention and then diagnostic capacity to 1ˢᵗ provide VL monitoring for early & appropriate drug Mx and 2ⁿᵈ HIV DR testing for both surveillance and clinical Mx

The global consequences of the HIV epidemic

There is evidence that supports a decline in global incidence both by UNAIDS

The corrected GBD analysis estimates the global prevalence lower than that of UNAIDS

With both methods showing a decline in HIV related deaths.

Global HIV incidence (A), prevalence (B), and mortality (C), 1990—2013, for all ages and both sexes combined Shaded areas are 95% uncertainty intervals.


A Global incidence

B Prevalence

C Deaths
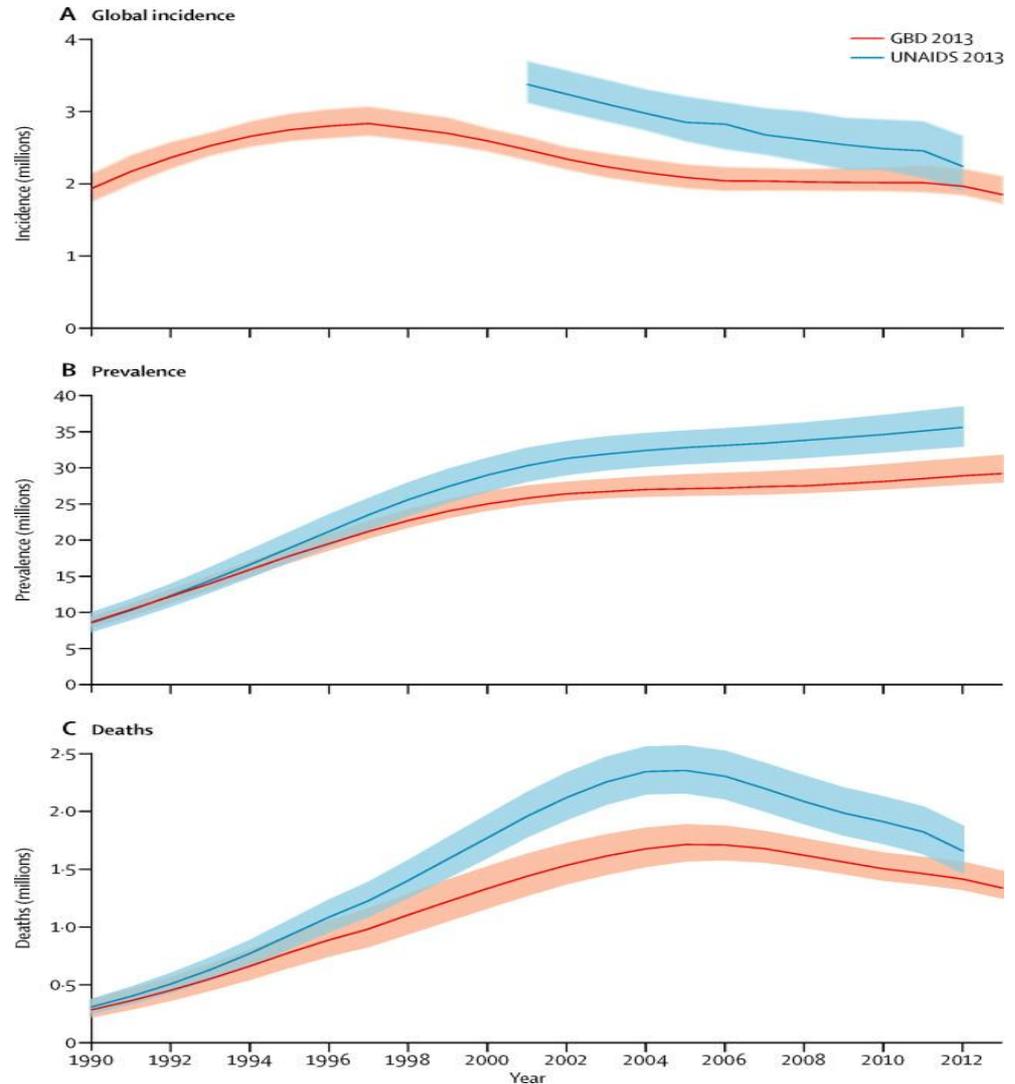
Increasing ART coverage

Number of people receiving antiretroviral therapy newly added during 2010-2013

- 33% South Africa
- 7% India
- 6% Uganda
- 5% Zimbabwe
- 5% Nigeria
- 5% Mozambique
- 5% United Republic of Tanzania
- 4% Zambia
- 4% Kenya
- 4% Malawi
- 22% Remaining countries
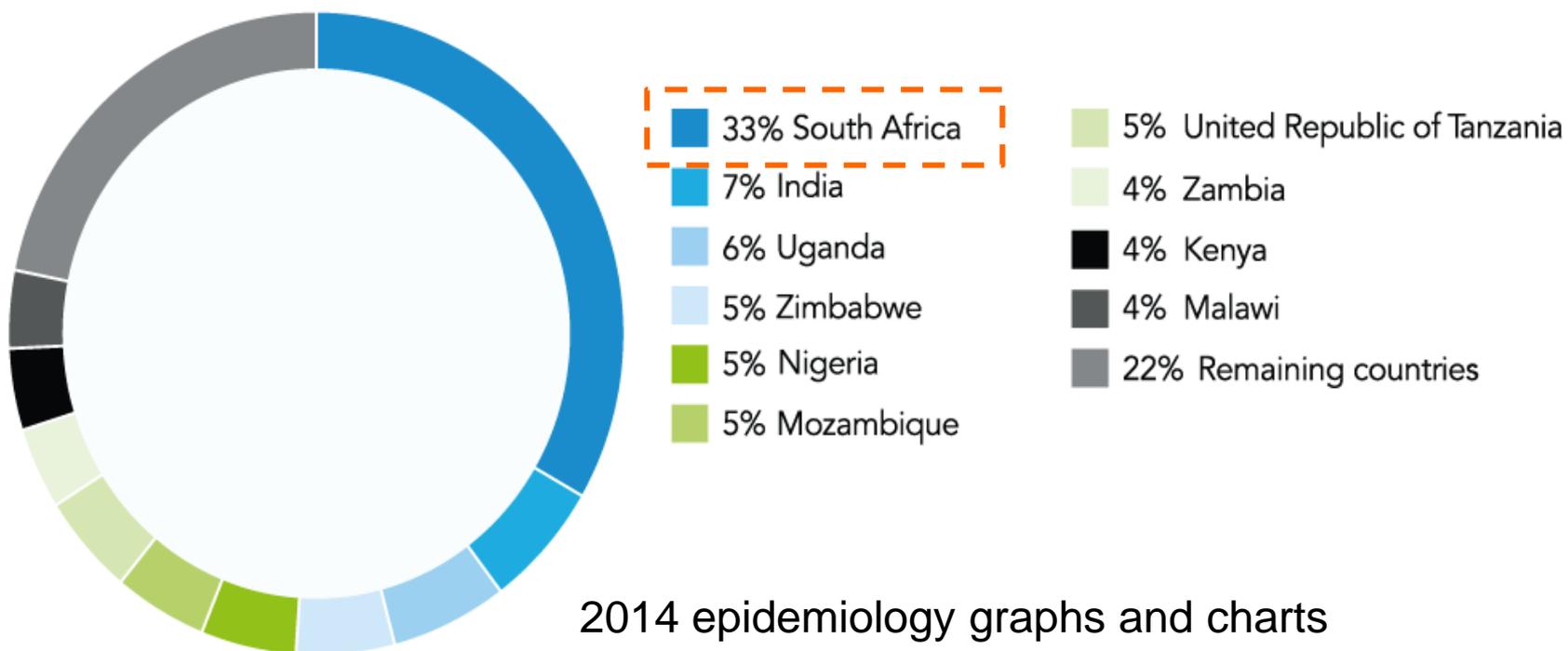
2014 epidemiology graphs and charts

Projected impact of highly active antiretroviral therapy on expected survival of a 20-year-old person living with HIV in a high-income country consider in different time periods
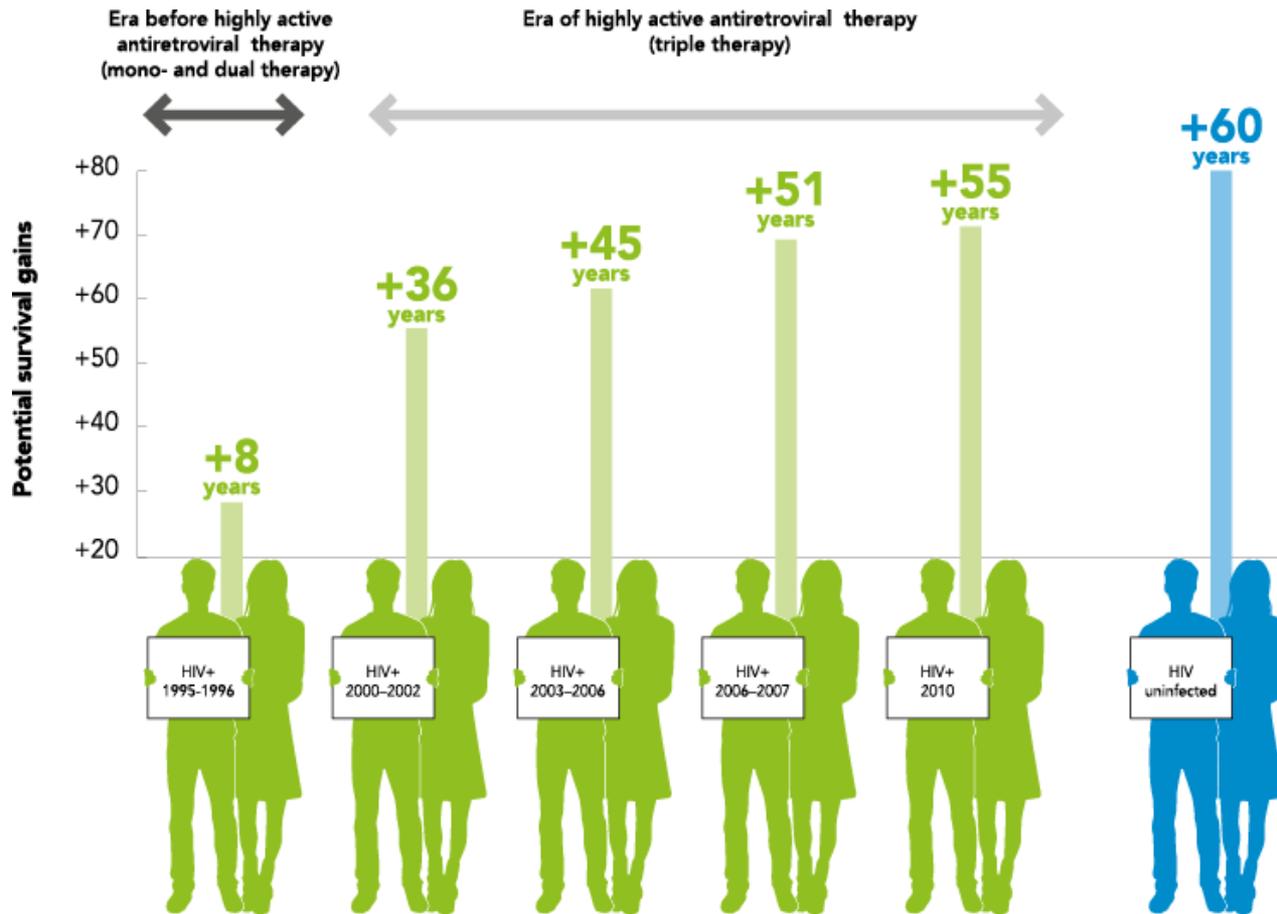
SA has an algorithm that includes viral load assessment as a ARV monitoring parameter.

Standardised national eligibility criteria for starting ART regimens for adults and adolescents have been set in SA
Fast tracking of specific population groups e.g pregnant women, children under 2, etc.

? 500 cell/mL

Eligible to start Lifelong ART
- CD4 count <350 cells/mm3 irrespective of WHO clinical stage
OR
- Irrespective of CD4 count
o All types of TB (In patients with TB drug resistant or sensitive, including extra pulmonary TB)
- WHO stage 3 or 4 irrespective of CD4 count

Require fast track (i.e. ART initiation within 7 days of being eligible)
- HIV positive women who are pregnant or breast feeding
OR
- Patients with low CD4 <200
OR
- Patients with Stage 4, irrespective of CD4 count
OR
- Patients with TB/HIV co morbidity with CD4 count < 50
(Patients with Cryptococcus meningitis or TB meningitis (defer ART for 4-6 weeks)

Patients with CD4 above 350, Not yet eligible for ART
- Transfer to a wellness programme for regular follow-up and repeat CD4 testing 6-monthly.
- Advise on how to avoid HIV transmission to sexual partners and children
- Initiate INH prophylaxis if asymptomatic for TB
- Provide counselling on nutrition and contraception and do annual pap smear

Source: SA ART Guidelines, NDoH

Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection: a multicentre retrospective cohort study

The TenoRes Study Group*

Summary

Background Antiretroviral therapy (ART) is crucial for controlling HIV-1 infection through wide-scale treatment as prevention and pre-exposure prophylaxis (PrEP). Potent tenofovir disoproxil fumarate-containing regimens are increasingly used to treat and prevent HIV, although few data exist for frequency and risk factors of acquired drug resistance in regions hardest hit by the HIV pandemic. We aimed to do a global assessment of drug resistance after virological failure with first-line tenofovir-containing ART.

**Interpretation** We recorded drug resistance in a high proportion of patients after virological failure on a tenofovir-containing first-line regimen across low-income and middle-income regions. Effective surveillance for transmission of drug resistance is crucial.

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Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection: a multicentre retrospective cohort study
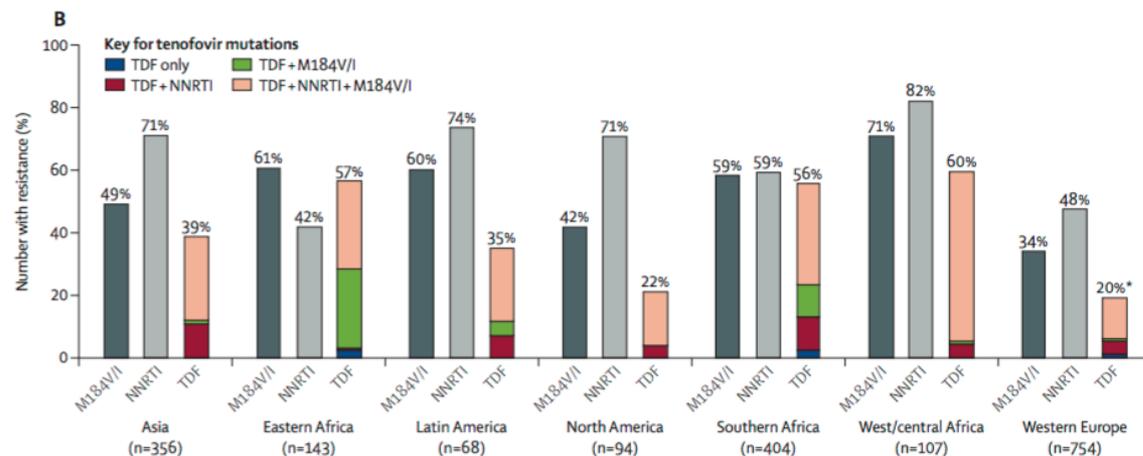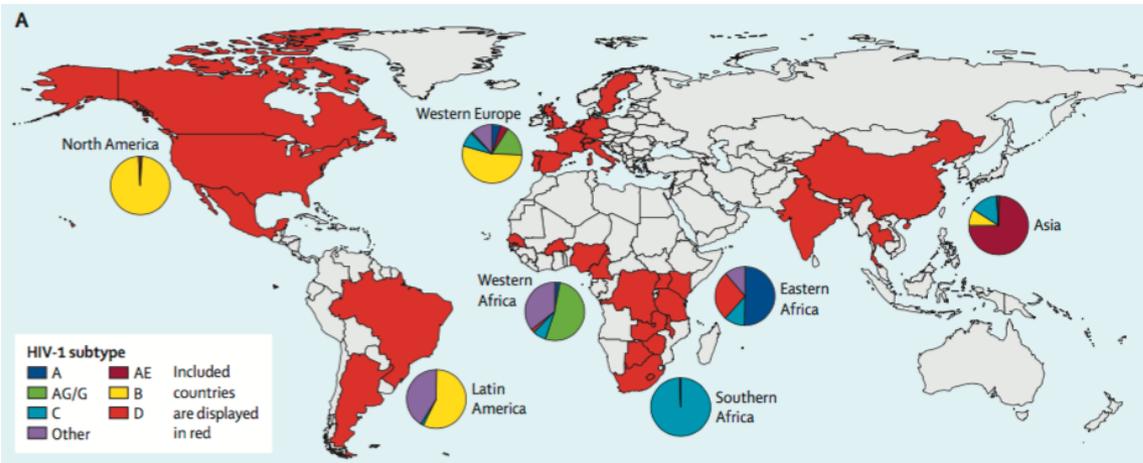
- 1926 patients from 36 countries with **treatment failure** between 1998 and 2015.
- **Prevalence** of tenofovir resistance was highest in sub-Saharan Africa (370/654 [57%]).
- Pre-ART CD4 cell count was the covariate most strongly associated with the development of tenofovir resistance (odds ratio [OR] 1·50, 95% CI 1·27–1·77 for CD4 cell count <100 cells per µL).

Lancet Infect Dis 2016

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Global trends in antiretroviral resistance in treatment-naive individuals with HIV after rollout of antiretroviral treatment in resource-limited settings: a global collaborative study and meta-regression analysis

Ravindra K Gupta, Michael R Jordan, Binta J Sultan, Andrew Hill, Daniel H J Davis, John Gregson, Anthony W Sawyer, Raph L Hamers, Nicaise Ndembi, Deenan Pillay, Silvia Bertagnolio

Interpretation Our findings suggest a significant increase in prevalence of drug resistance over time since antiretroviral rollout in regions of sub-Saharan Africa; this rise is driven by NNRTI resistance in studies from east and southern Africa. The findings are of concern and draw attention to the need for enhanced surveillance and drug-resistance prevention efforts by national HIV treatment programmes. Nevertheless, estimated levels, although increasing, are not unexpected in view of the large expansion of antiretroviral treatment coverage seen in low-income and middle-income countries—no changes in antiretroviral treatment guidelines are warranted at the moment.

Prevalence of drug resistance in treatment-naive trial participants with HIV-1, by time since antiretroviral rollout

(A) East Africa.

(B) Southern Africa.
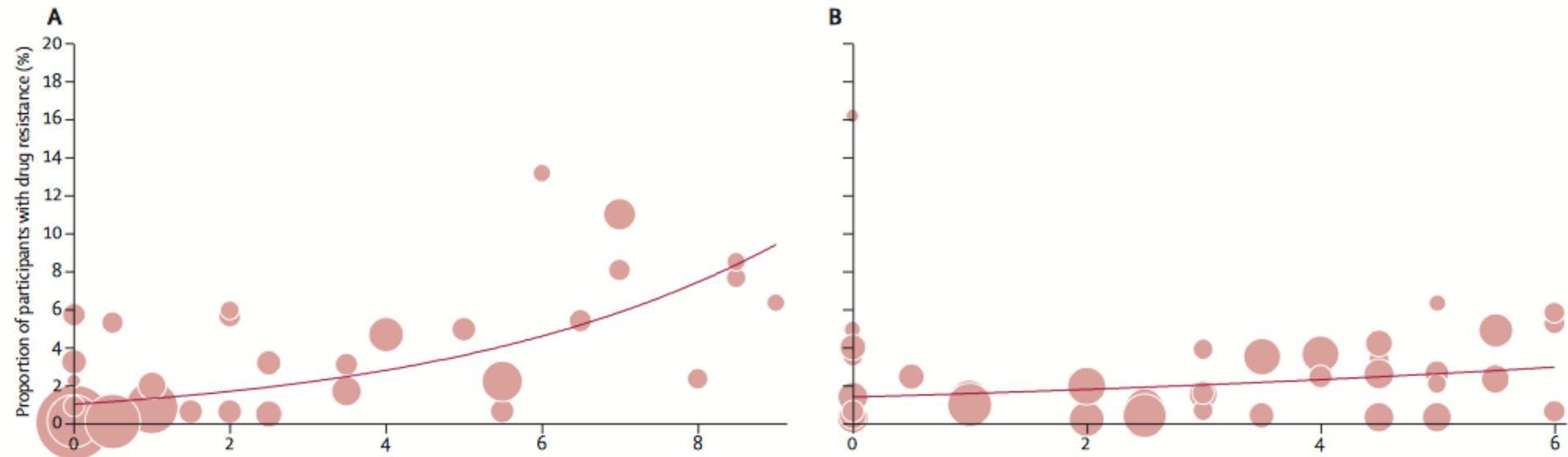
Every circle is a study and the size of the circle is proportional to the precision of the estimate from the individual study, with sizes comparable within individual graphs only. The trend line is predicted prevalence.

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Prevalence of major drug-resistance mutations that confer resistance to non-nucleoside reverse transcriptase inhibitors, by time since antiretroviral rollout in east Africa

Size of circle is proportional to the precision of the estimate from the individual study

The trend line is predicted prevalence
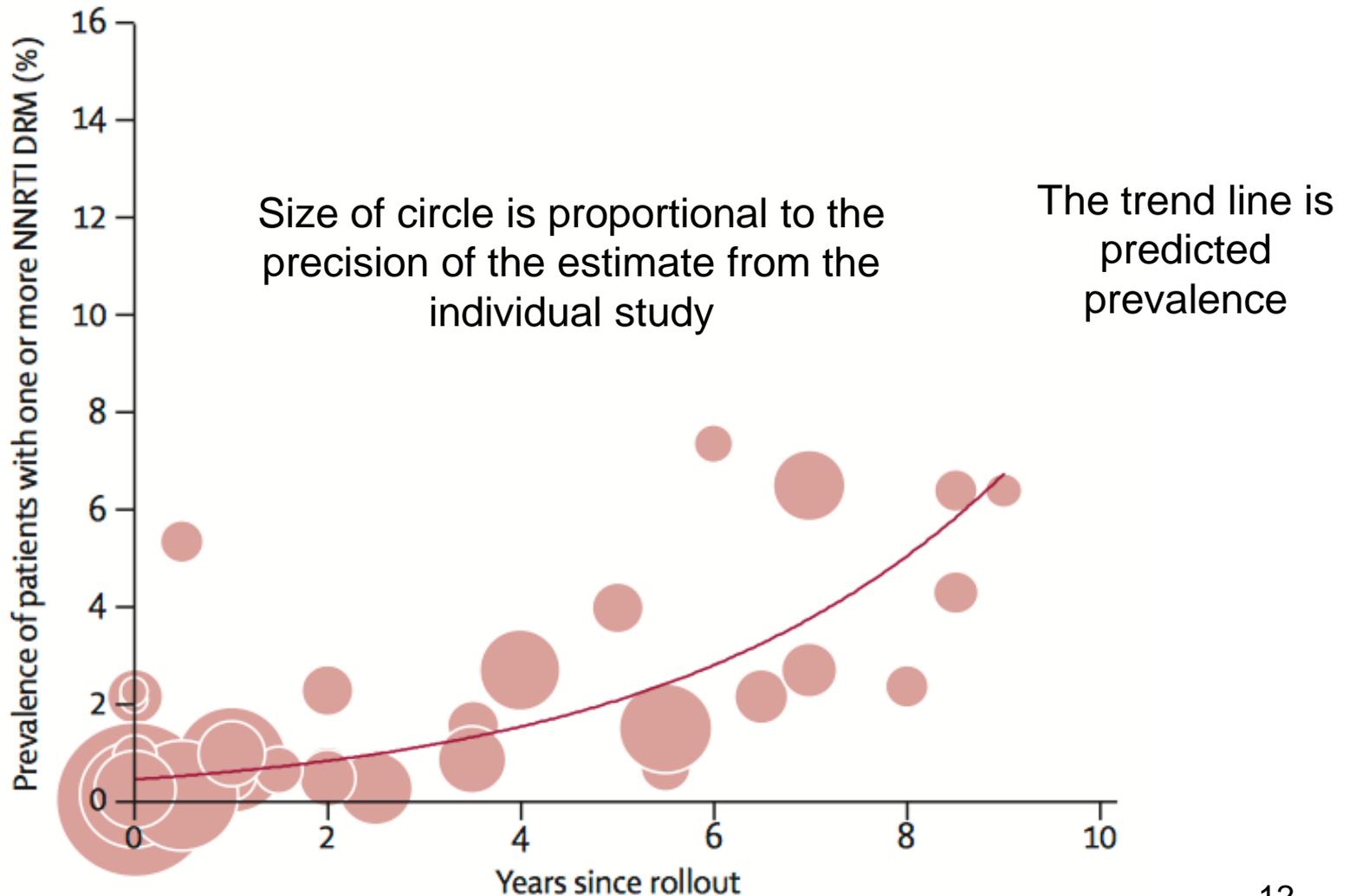
HIV-1 drug resistance in antiretroviral-naive individuals in sub-Saharan Africa after rollout of antiretroviral therapy: a multicentre observational study
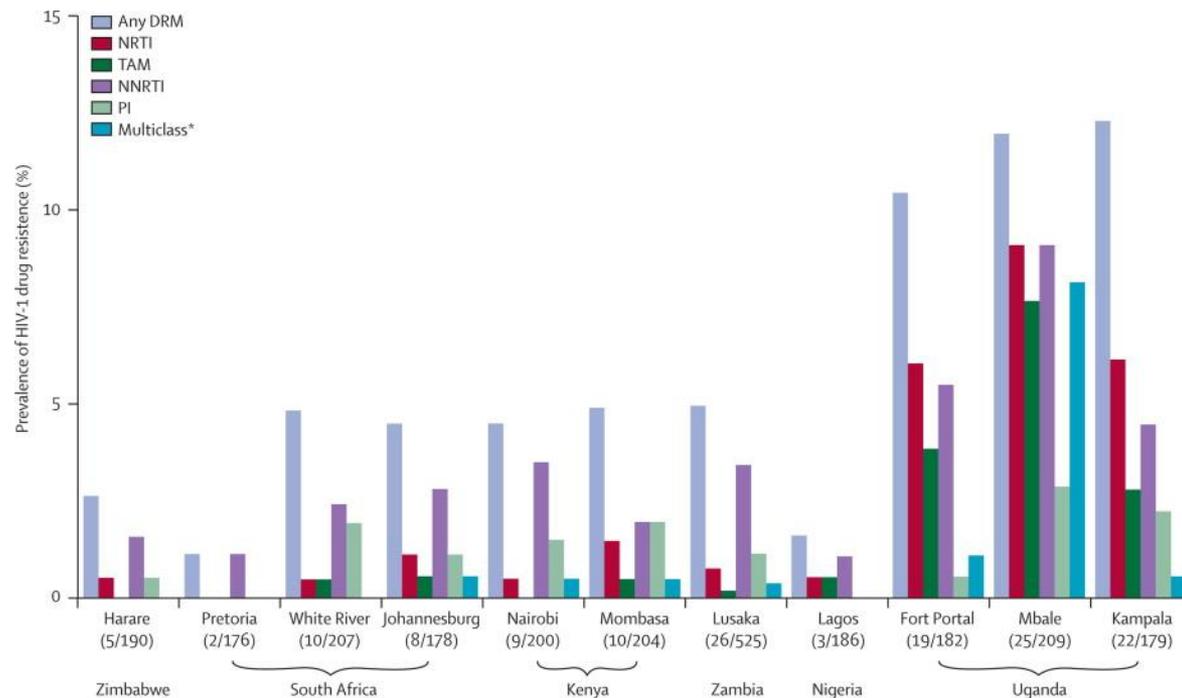
Prevalence of HIV-1 primary drug-resistance in antiretroviral-naive individuals in the PASER-M cohort by region and drug class
People with at least one drug-resistance mutation shown as proportion of all people by region and drug class. Regions a...

ORIGINAL ARTICLE

Assessment of Second-Line Antiretroviral Regimens for HIV Therapy in Africa

Nicholas I. Paton, M.D., Cissy Kityo, M.Sc., Anne Hoppe, Ph.D.,
Andrew Reid, M.R.C.P., Andrew Kambugu, M.Med., Abbas Lugemwa, M.D.,

BACKGROUND

The efficacy and toxic effects of nucleoside reverse-transcriptase inhibitors (NRTIs) are uncertain when these agents are used with a protease inhibitor in second-line therapy for human immunodeficiency virus (HIV) infection in resource-limited settings. Removing the NRTIs or replacing them with raltegravir may provide a benefit.

ORIGINAL ARTICLE

Assessment of Second-Line Antiretroviral Regimens for HIV Therapy in Africa

RESULTS

Good HIV disease control was achieved in 60% of the patients (mean, 255 patients) in the NRTI group, 64% of the patients (mean, 277) in the raltegravir group (P=0.21 for the comparison with the NRTI group; superiority of raltegravir not shown), and 55% of the patients (mean, 232) in the monotherapy group (noninferiority of monotherapy not shown, based on a 10-percentage-point margin). There was no significant difference in rates of grade 3 or 4 adverse events among the three groups (P=0.82). The viral load was less than 400 copies per milliliter in 86% of patients in the NRTI group, 86% in the raltegravir group (P=0.97), and 61% in the monotherapy group (P<0.001).
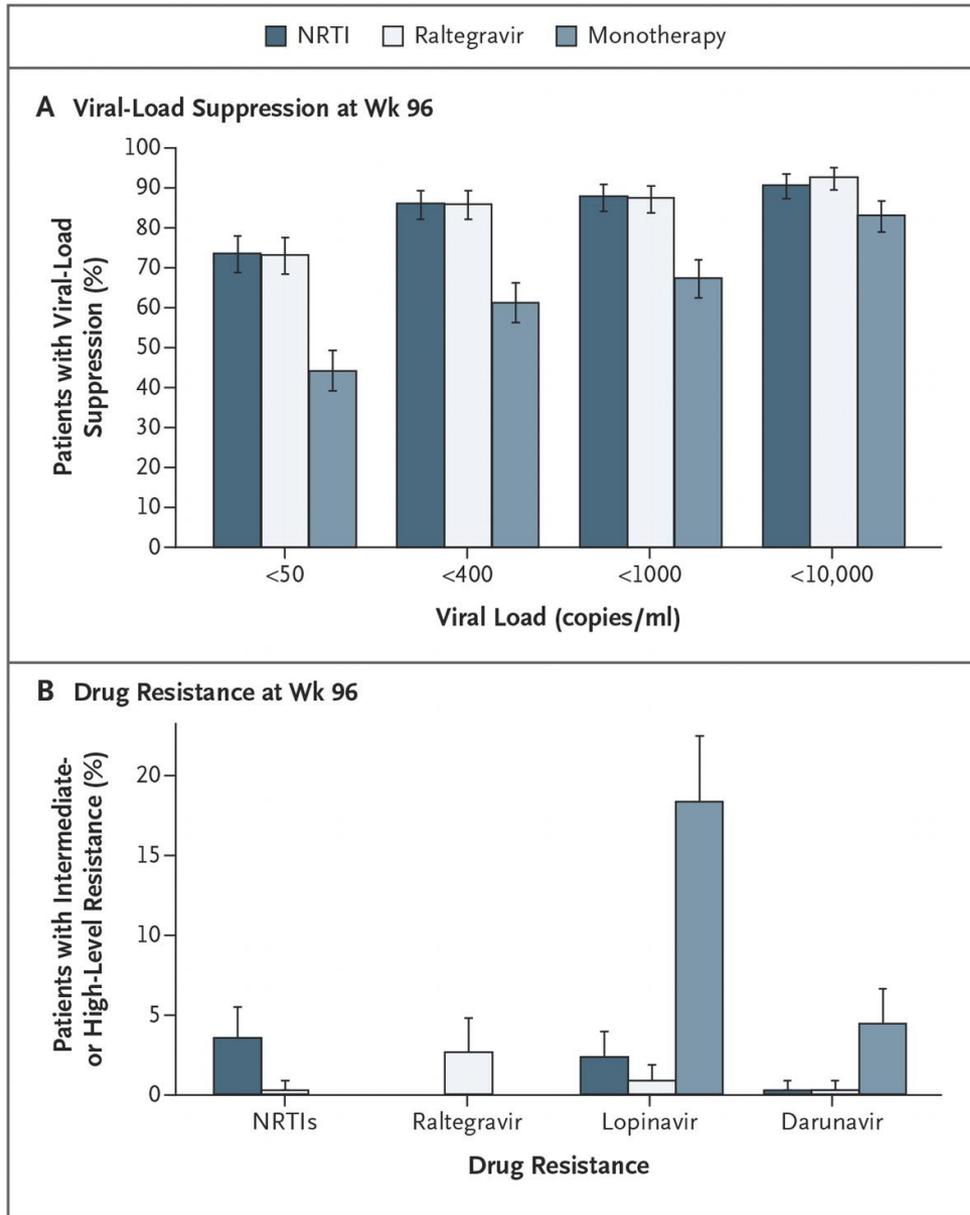
A Viral-Load Suppression at Wk 96

B Drug Resistance at Wk 96

Legend: NRTI, Raltegravir, Monotherapy

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ORIGINAL ARTICLE

Assessment of Second-Line Antiretroviral Regimens for HIV Therapy in Africa

CONCLUSIONS

When given with a protease inhibitor in second-line therapy, NRTIs retained substantial virologic activity without evidence of increased toxicity, and there was no advantage to replacing them with raltegravir. Virologic control was inferior with protease-inhibitor monotherapy. (Funded by European and Developing Countries Clinical Trials Partnership and others; EARNEST Current Controlled Trials number, ISRCTN 37737787, and ClinicalTrials.gov number, NCT00988039.)

Emergence of HIV Drug Resistance During First- and Second-Line Antiretroviral Therapy in Resource-Limited Settings

Mina C. Hosseinipour,[1,2] Ravindra K Gupta,[3] Gert Van Zyl,[4] Joseph J. Eron,[2] and Jean B. Nachega[5,6,7]

[1]University of North Carolina Project, Lilongwe, Malawi; [2]University of North Carolina School of Medicine, Department of Medicine, Chapel Hill; [3]Division of infection and Immunity, University College London Medical School, United Kingdom; [4]Division of Medical Virology, Department of Pathology, Stellenbosch University and National Health Laboratory Service, Cape Town, South Africa, [5]Department of Medicine and Center for Infectious Diseases, Stellenbosch University Faculty of Medicine and Health Sciences, Cape Town, South Africa; [6]Departments of International Health and Epidemiology,

Summary of Studies Describing Human Immunodeficiency Virus (HIV) Drug Resistance to Second-Line Therapy From Resource-Limited Settings

Variable	Wallis et al [54]	El-Khatib et al [55]	Saravanan et al [56]	Levison et al [57]	van Zyl et al [37]	Ferradini et al [58]	Maiga et al [59]	Reynolds et al [60]	Hosseinipour et al (unpublished data)
Country	South Africa	South Africa	India	South Africa	South Africa	Cambodia	Mali	Uganda	Malawi
PI(s)	LPV/r	LPV/r for 114 patients, ATZ/r for 1	ATZ/r for 47.6% of patients, IND/r for 44.8%, LPV/r for 7.5%	LPV/r	LPV/r	LPV/r	LPV/r	LPV/r	LPV/r
HIV sequenced, % of patients	75	35	45	33	33	4	93	6	12
Duration of second-line therapy, mo	16		>6	10		≥24	≥48		12
Wild-type virus, patients, %	39	NR	NR	67	NR	25	20	NR	58
Major PI mutation								0	
Patients, %	7	6	≥49	0	6	50	28	0	16
Mutations	M46I, L76V, V82A	Q58E, M46L, L90M, N88S	M46I, I54V/A, V82A, L90M	. . .	NR	NR	12L76V,[a] M46I/L, I47V/A, I54M/L, Q58E, V82A/F/T/S, I84V, L90M	. . .	NR

Abbreviations: ATV/r, ritonavir-boosted atazanavir; IND/r, ritonavir-boosted indinavir; LPV/r, ritonavir-boosted lopinavir; NR, not reported; PI, protease inhibitor.

[a] Detected in 12% of patients.

The strategy needs to be simple

With the aim of having 90% of infected individuals on Rx and 90% of these viralogically suppressed we need to prevent HIV DR from developing:

i) EWI that looks at prevention of DR
ii) HIV DR surveys that monitor systematically the emergence of DR at a public health level and inform new regimens in the future
iii) Expansion of VL monitoring will ID virological failure promptly and trigger drug changes following adherence counseling
iv) DR testing for clinical management
v) Data driven monitoring of DR at a national level
vi) Maintain a national working group

The rationale for an HIVDR testing strategy

- Previously there was no coordinated national strategy for the surveillance of HIVDR

- The main goal of such a strategy would be to ***reduce HIV drug resistance across South Africa*** by both preventing the emergence of resistance and reducing the transmission of resistant strains. This can be done through the:

  - Establishment and implementation of a national HIVDR surveillance strategy as the foundation to guide programme decision making

  - Standardization of HIVDR testing practices (clinical and laboratory)

  - Gradual introduction of resistance testing into clinical practice and integration with clinical management guidelines

  - Development of a national Drug Resistance database for improved monitoring, evaluation and reporting

Prevention, surveillance and monitoring of HIV drug resistance are critical to the success of clinical and public health HIV/AIDS programmes in South Africa

Integrating drug resistance surveillance into the overall ART programme is the key to a sustainable strategy

The national HIVDR monitoring and prevention strategy must be integrated into the national HIV care and treatment strategy

Coordination, analysis and interpretation of national HIVDR data in the context of the entire treatment programme

Real-time monitoring of HIVDR development to assess treatment strategies in terms of HIVDR prevention

Support optimal use of available ARVs and guide population-based selection of current regimens

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The strategy rests on 4 key pillars:

Prevention of DR

EWI
(VL monito-ring
"3rd 90")

HIV DR Clinical Mx

HIVDR Surveill-ance

Data Manage-ment MnE Reporting

Prevention, attention to early warning indicators, capacitation of HIVDR for individual patient management, strengthening surveillance and prompt reporting on national data

Early Warning

The WHO early warning indicators

Early Warning Indicator	Target
1. On-time pill pick-up	**<80%** **80 -90%** **>90%**
2. Retention in care	**<75% retained after 12 months of ART** **75 – 85% retained after 12 months of ART** **>85% retained after 12 months of ART**
3. Pharmacy stock-outs	**<100% of a 12-month period with no stock-outs** **100% of a 12-month period with no stock-outs**
4. Dispensing practices	**>0% dispensing of mono- or dual therapy** **0% dispensing of mono- or dual therapy**
5. Viral load suppression at 12 months	**<70% viral load suppression after 12 months of ART** **70 – 85% viral load suppression after 12 months of ART** **>85% viral load suppression after 12 month of ART**

RED: Poor performance, below the desired level;
AMBER: Fair performance, not yet at desired level;
GREEN: Excellent performance, achieving desired level

WHO global strategy for surveillance and monitoring of HIVDR 2012

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The strategy rests on 4 key pillars:
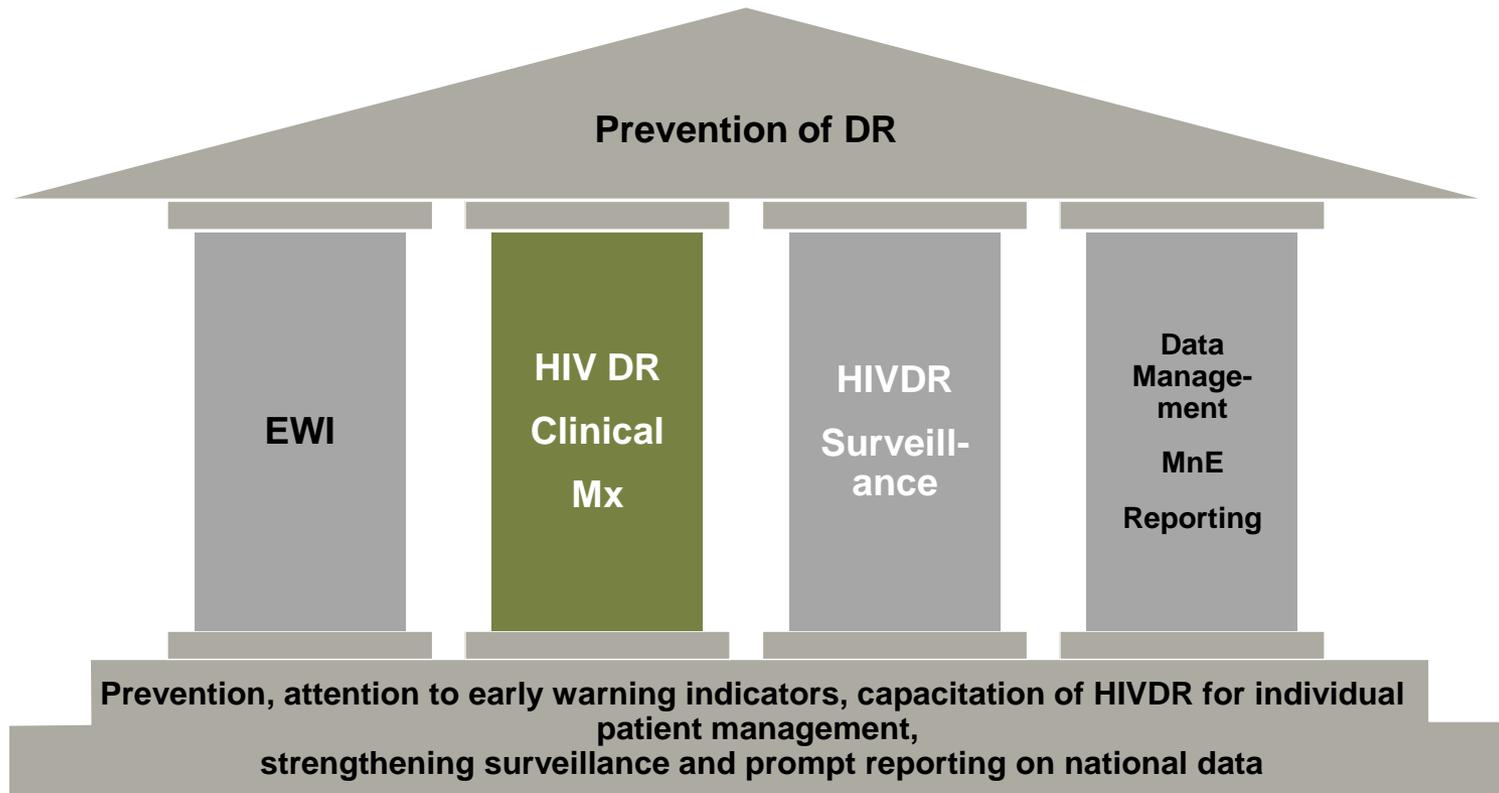
Clinical Care

From patient to public health :
Expanding HIVDR testing in order to better manage HIV in the South African context

- There are 5 HIVDR testing laboratories in the country, with a total estimated testing capacity of ~3000 tests/annum, with the majority of the diagnostic testing conducted by two NHLS laboratories, namely Charlotte Maxeke, Johannesburg and Tygerberg, Stellenbosch laboratories

- The testing capacity needs to be increased from 3000 tests/annum to ~100 000 tests/annum

- This goal can only be reached by both increasing the number of labs that can perform HIVDR testing with the adequate trained personnel and by looking at new testing platforms which can increase the throughput

- Global Fund Phase 1 has focused on increasing the testing capacity at the existing labs in Johannesburg and Stellenbosch

- Phase 2 of the Global Fund proposal aims to further increase the capacity by strengthening 3 existing facilities in strategic areas of high prevalence to ensure national coverage

Objective 3: To develop adequate capacity to address the increasing need for HIVDR testing, clinical interpretation and management

- The use of genotypic resistance testing to guide the switch to second-line and third-line ART regimens for adults needs to be a cost-effective strategy in the context of the SA national ART programme

- This will need to be coupled with specific training on the interpretation of assay results
  - This will take place initially by referral to specialized centers that will manage second and third-line failures

- Resistance testing will be increasingly required to inform clinical- decision making for children, who are particularly vulnerable

- HIVDR testing is becoming more affordable and more accessible with developments in technology and with the expansion of laboratory capacity within the country

Opportunity:

To build the capacity in the public health system to integrate genotypic resistance testing into existing clinical management algorithms

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BMC Genomics

RESEARCH ARTICLE

Open Access

Comparison of three next-generation sequencing platforms for metagenomic sequencing and identification of pathogens in blood

Kenneth G Frey[1,2], Jesus Enrique Herrera-Galeano[1,2], Cassie L Redden[1,2], Truong V Luu[1,2], Stephanie L Servetas[3], Alfred J Mateczun[1], Vishwesh P Mokashi[1] and Kimberly A Bishop-Lilly[1,2*]

Conclusion:

The analytical sensitivity of all three platforms approaches that of standard qPCR assays.

Although all platforms were able to detect pathogens at the levels tested, there were several noteworthy differences.

Roche-454 Titanium platform produced consistently longer reads, even when compared with the latest chemistry updates for the PGM platform.

MiSeq platform produced consistently greater depth and breadth of coverage

Ion Torrent was unequaled for speed of sequencing….

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Next Generation Sequencing platforms

Instrument	Time	Read length	Lanes	Max #reads	Max cap.
Roche GS-FLX	10 h	500 bp	2/4/8/16	10^6	500 Mbp
Roche GS-Junior	10 h	500 bp	1	$70*10^3$	35 Mbp
Illumina HiSeq*	14 days	$1*35 - 2*100$ bp	2*8	$3*10^9$	> 600 Gbp
Illumina MiSeq	5.5 – 40 h	$1*50 - 2*250$ bp	1	$15*10^6$	> 7.5 Gbp
Ion Torrent PGM	2.4 - 4.5 h	200 bp (soon 400)	1	10^5 (314 chip)	20 Mbp
				10^6 (316 chip)	200 Mbp
				$5*10^6$ (318 chip)	1.000 Mbp

The strategy rests on 4 key pillars:
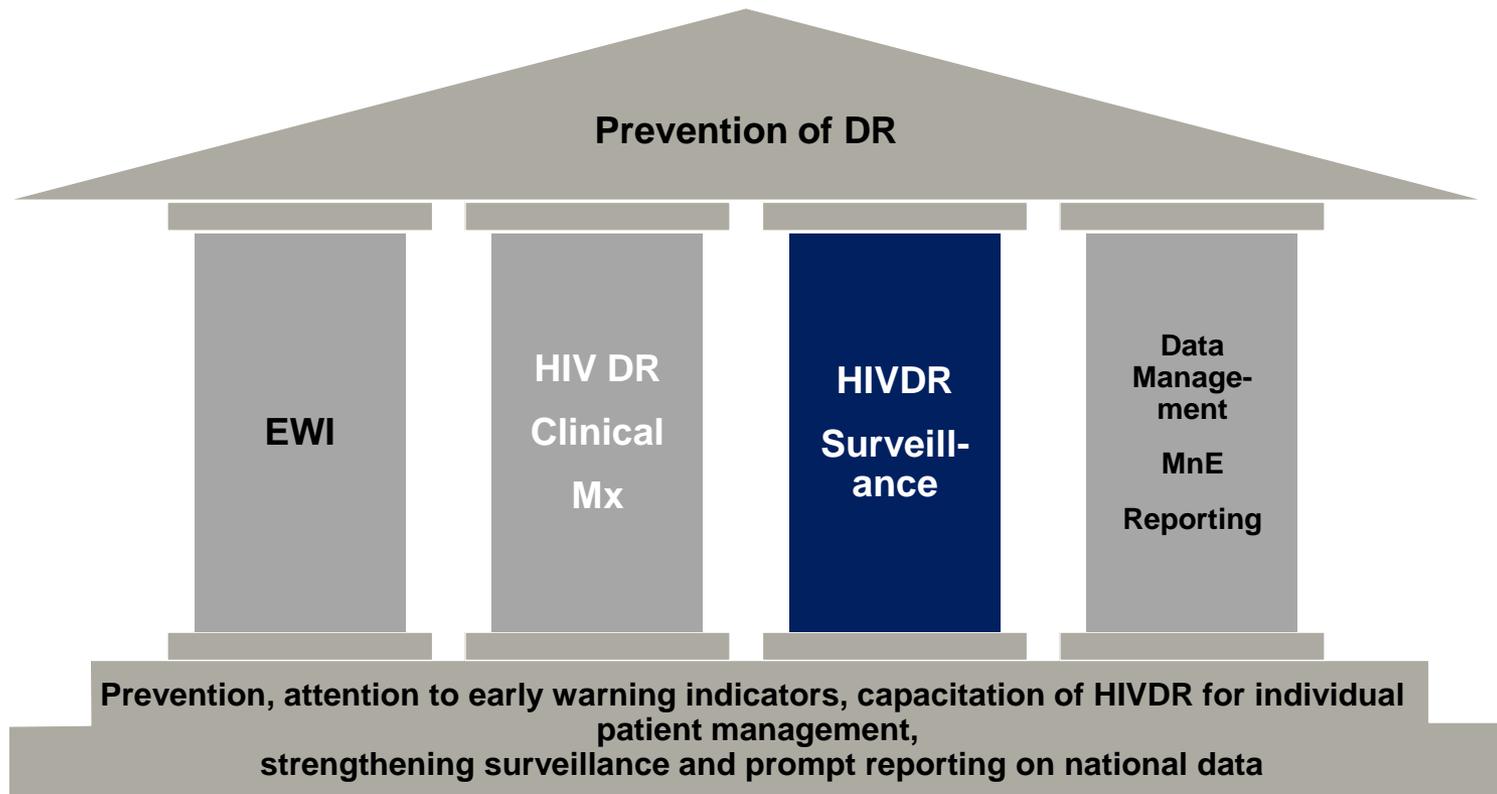
Surveillance

Integration of Elements of Global Strategy

Monitor acquired HIVDR in patients on ART

Acquired HIVDR Surveys

Classify transmitted HIVDR among newly infected patients

Transmitted HIVDR Surveys

Estimate HIVDR in children < 18 months of age

Pediatric Surveys

Monitor program factors associated with emergence of HIVDR

Early Warning Indicators

National HIVDR evidence base

Pre-treatment HIVDR surveys

Results lead to **programmatic action** to:
• Minimize emergence and transmission of HIVDR
• Optimize quality of patient care
• Select population-based ART regimens

World Health Organization

To monitor the drug resistance patterns in South Africa through surveillance

- Increasing concerns about HIV drug resistance make the monitoring of resistance to ARV on a population basis a high priority

- Minimizing drug resistance on a programmatic level is of national importance

- HIV drug resistance surveillance and monitoring systems provide HIV drug resistance information for the following purposes:

  – To enable education and prevention programmes to address increasing rates or high prevalence of drug resistance

  – To support rational use of antiretroviral drugs by treatment programme planners and individual clinicians

  – To support the development and revision of treatment guidelines

  – To provide a resource for addressing important questions on HIV drug resistance patterns and spread

HIVDR testing for individual clinical management

- **The South African Antiretroviral Treatment Guidelines (2013)** state that only patients failing 2nd line therapy should be managed by an expert panel, using HIVDR testing

- The switch to a third line therapy should be expert and HIVDR testing based decision and requires supervised care

- **The 2012 southern African ARV drug resistance testing guidelines** do not recommend resistance testing in HIV-infected adults upon diagnosis or ART initiation

- However, baseline resistance testing is recommended for children who have been exposed to ART for prevention of mother-to-child-transmission therapy and subsequently become HIV-infected

- Resistance testing is also recommended after virological failure of first- and second-line ART regimens

Using HIVDR testing to inform guidelines and improve broad-scale HIV management

- Surveillance HIVDR data acquired from sentinel surveillance in the country will directly inform policy makers on appropriate ART guidelines

- HIVDR data generated from routine testing of patients failing 2nd line ART will be informative to assess the:

  - Ongoing trend analysis of HIVDR
 - Optimizes strategies for 3rd line and salvage regimens

Surveillance of HIVDR: Transmitted DR

Province	# sequences	# with mutations (1st 47)	NRTI threshold level	NNRTI threshold level	# with mutations total	NRTI Point prevalence (95% CI)	NNRTI Point Prevalence (95% CI)
GP	54	2	<5%	<5%	2	1.9% (0.3 - 10.1%)	1.9% (0.3 - 10.1%)
KZN	62	2	<5%	5-15%	2	0	3.2% (0.9 - 11.0%)
OFS	67	2	<5%	5-15%	2	0	3.0% (0.8 - 10.3%)
EC	85	2	<5%	5-15%	3	1.5% (0.3 - 8.0%)	3.5% (1.2 - 9.9%)
WC	79	1	<5%	<5%	4	2.6% (0.7 - 9.0%)	3.9% (1.3 - 10.9%)

Country	Geographical area	2004	2005	2006	2007	2008	2009	2010
Botswana	Francistown							
Malawi	Lilongwe						NNRTI	NNRTI
South Africa	Gauteng	NRTI						
South Africa	KwaZulu-Natal					NNRTI +NRTI	NNRTI	NNRTI +NRTI
Swaziland	Manzini-Mbambane corridor							
Uganda	Entebbe/Kampala[b]						NRTI	
China	Beijing							
China	Hunan						NNRTI	
China	Liangshan (Sichuan)							
China	Shenzhen							

Surveillance of transmitted HIV drug resistance in SA

HIV prevalence estimates: 2011 ANSUR survey
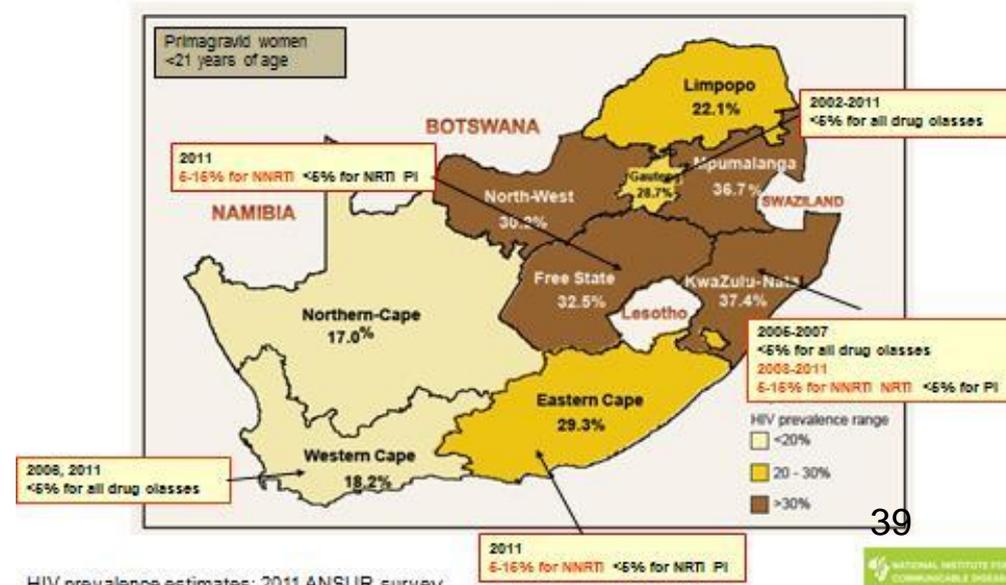
# Surveillance of HIVDR: Acquired DR

Global fund survey

- Nation-wide sentinel surveillance survey representative sample based on ART coverage per province
- To assess the HIVDR prevalence and specific resistance patterns in patients
  - Adult patients failing 1st line regimens (NNRTI based): n=900
  - Adult patients failing 2nd line regimens (PI-based): n= 450
  - Adult patients initiating ARVs: n=336
  - < 18mo EID + (WHO PPS Protocol)
- Strengthen lab capacity across 2 sites initially and a further 3 in phase 2

KZN pilot ADR survey

- To estimate the proportion of adult patients failing 1st-line ART after 1 year and after 2 years on treatment, and the proportion of paediatric patients failing first-line ART at 15 ART clinics in KZN
- To describe the patterns of HIV DRM in patients with detectable viral load
- To provide representative data about HIVDR in KZN Province to guide provincial and national HIVDR strategy
- Cross sectional
- 3120 specimens (1766 collected to date)
- VL and genotype if >1000cpm

Figure 4.7 HIV drug resistance among people experiencing treatment failure at 12 months, by drug and drug class

40
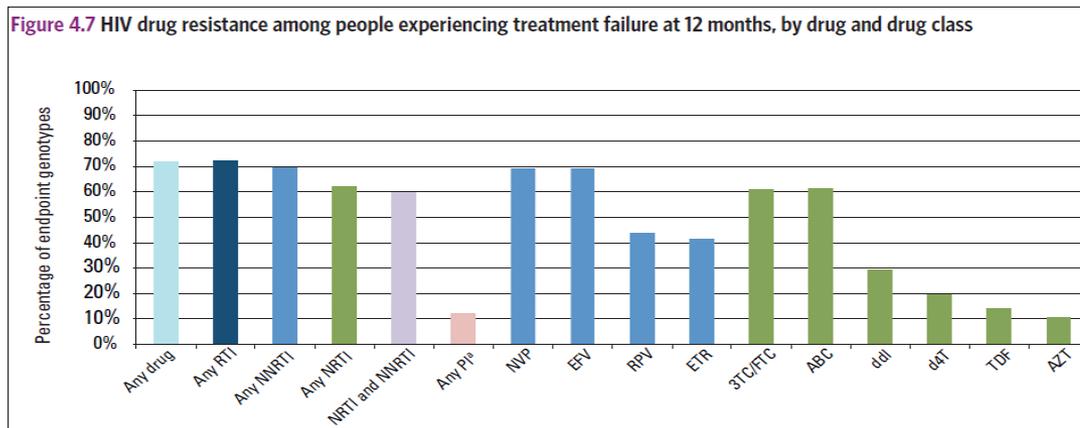
Surveillance of HIVDR: Pre-treatment

The strategy rests on 4 key pillars:

Prevention of DR

| EWI | HIV DR Clinical Mx | HIVDR Surveill-ance | Data Manage-ment MnE Reporting |

Prevention, attention to early warning indicators, capacitation of HIVDR for individual patient management, strengthening surveillance and prompt reporting on national data
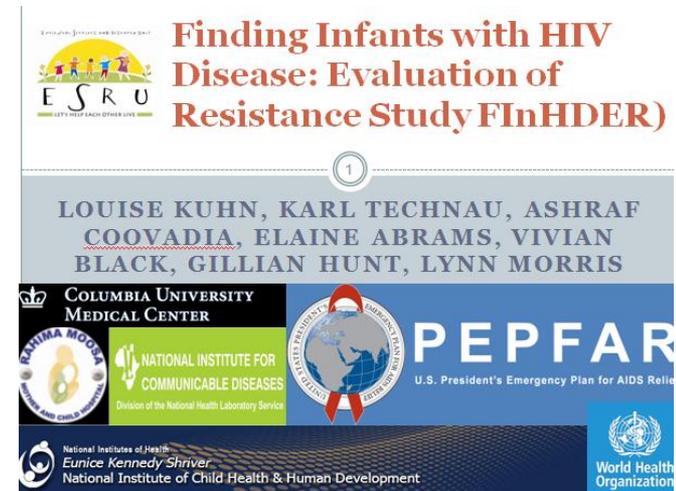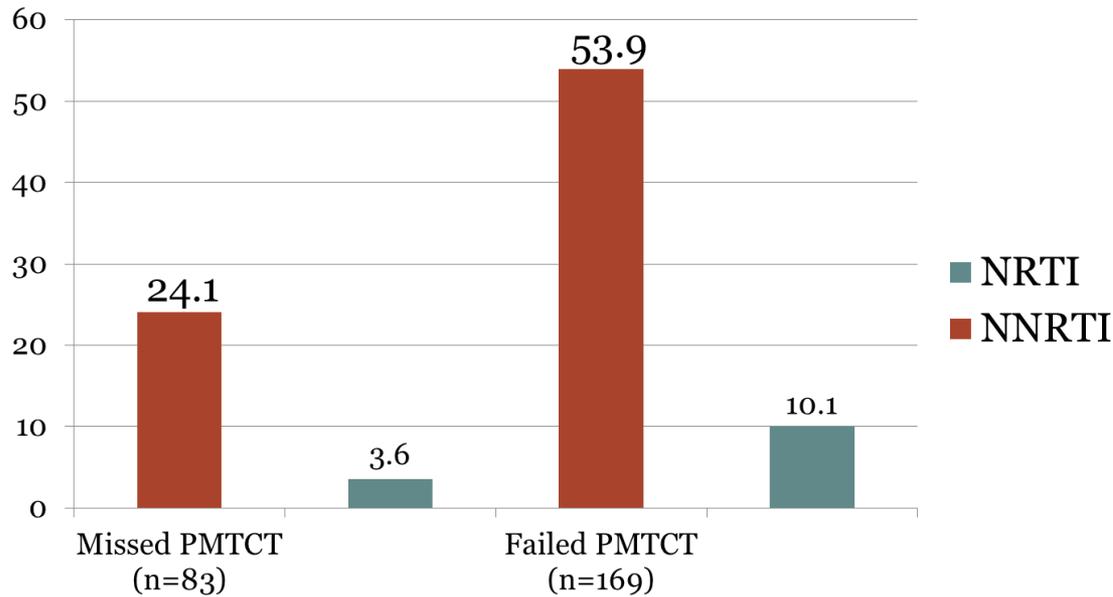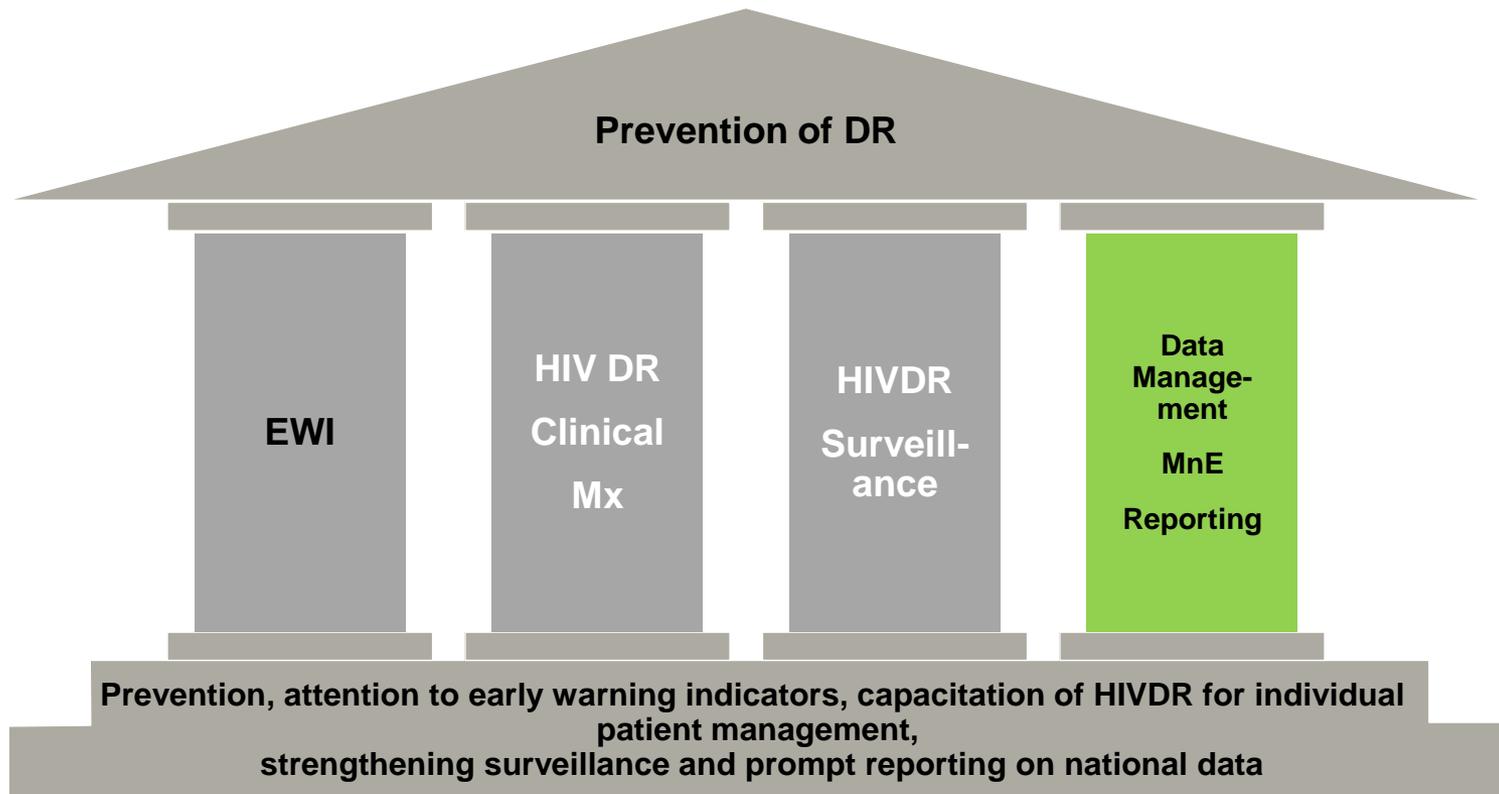
Big Data management

Objective 4: Strengthen the monitoring and evaluation of the HIVDR strategy by establishing a central data repository and reporting and epidemiological analysis

- Comprehensive, accurate and robust analyses of HIV drug resistance data are essential for guiding ART policies

- One of the key components of a successful national plan for HIV drug resistance is to have a central database that can curate, store, analyze and distribute resistance data in an accurate and timely manner

- To establish a centralized database, consideration needs to be given to the following:
  - The need to define the minimum standard information to be reported to the central database from are a number of drug resistance database systems available in SA

  - The need to define the frequency with which the minimum information is uploaded

  - A memorandum of operation and access policy to be developed for each database

  - The working group to prepare regular reports to the NDoH on the levels of resistance and impact on first-, second- and third-line regimens

  - Development of dashboards for purposes of easy programme monitoring which allows the identification of drug resistance hot spots

Using surveillance data to inform public health decisions

- Data management , generation of reports and assessment of the public health implications of the analysis.

- There will be an agreed set of minimum standards

Putting the right systems in place: Data management and monitoring and evaluation

- e.g. dashboards will be generate to view and interrogate the data.
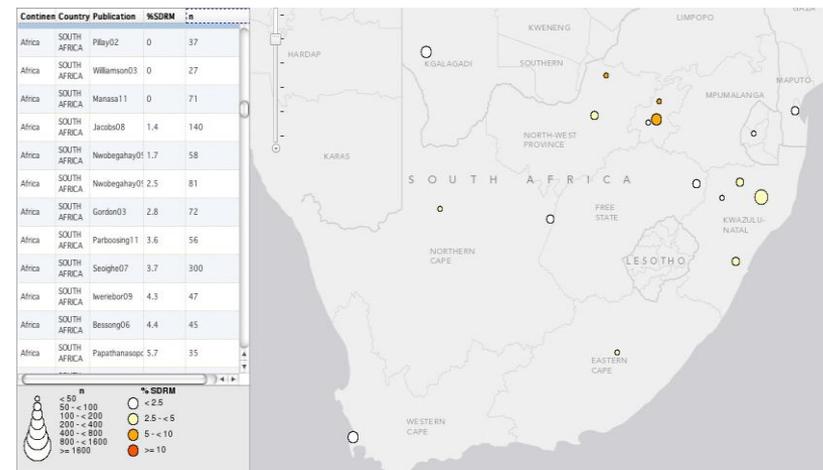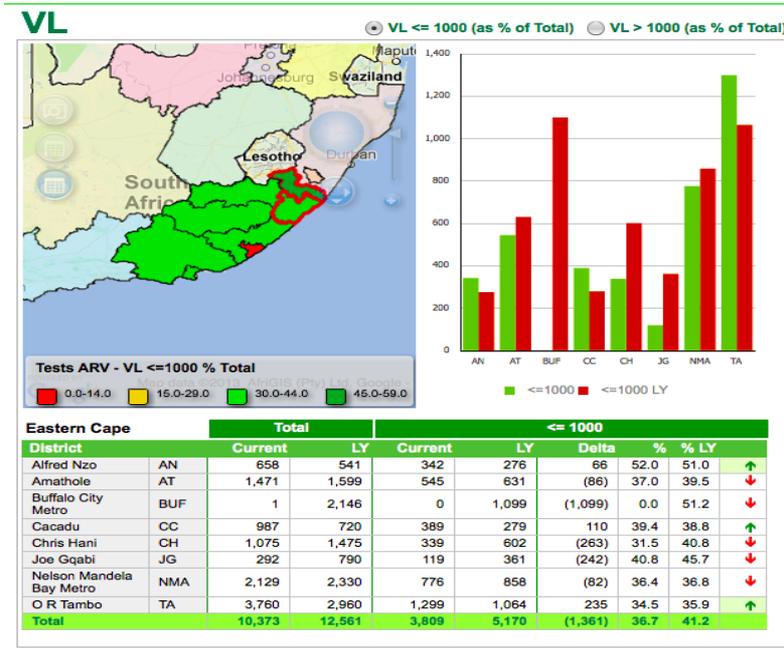
HIV-1 drug resistance in ARV-naive populations. The dashboard is a compendium of published virus sequences from 32,290 persons, 213 studies according to region, year and subtype. Of these studies, 13 are from South Africa, showing transmitted drug resistance level ranging from 0% to <10%