Impact of ART resistance in sub Saharan Africa

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US Centers for Disease Control and Prevention

ITREMA Resistance Training Workshop

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Background

- **ART in sub Saharan Africa is marked by:**
  - Limited lines of regimens
  - Reduced access to routine viral load monitoring
  - Limited access to resistance testing

These limitations magnify the importance of HIVDR considerations in this setting

Key Questions

- **What is the risk of HIVDR (and impact on treatment success) in PLHIV:**
  - Starting ART?
  - Restarting ART?
  - Failing NNRTI-based ART?
  - Failing DTG-based ART?
  - Failing PI-based ART?

Individual vs Population risk of HIVDR

- **Individual risk: uses drug resistance testing to determine the presence or absence of HIVDR and, when present, allows clinical provider to tailor the regimen to that individual**
- **Population risk: uses surveillance and other observational cohort/research data to determine the likelihood that an individual patient will have HIVDR**
  - For an individual patient
    - if the likelihood of HIVDR is high, clinicians (or clinical guidelines) should treat as if HIVDR is present
    - If the likelihood of HIVDR is low, then treat as if HIVDR absent
      - But how low????

Key Questions: Individual Risk

- **Pre-ART drug resistance (PDR)**
  - NNRTI resistance more common than NRTI resistance
  - NNRTI resistance more likely with history of prior ART exposure
  - In the presence of NNRTI resistance patient is likely to fail so alternative regimen should be used (PI- or INSTI-based)
    - Not all patients fail but most do and early viral suppression may not be sustained

Key Questions: Individual Risk

- **HIVDR in persons with treatment failure**
  - Treatment failure could be defined as a single viral load elevation or two consecutive elevated measurements
  - If failing NNRTI-based
    - 60-90% have NNRTI resistance

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HIV DRUG RESISTANCE DATABASE

A curated public database to represent, store and analyze HIV drug resistance data.

HOME | GENOTYPE-RX | GENOTYPE-PHENO | GENOTYPE-CLINICAL | HIVdb PROGRAM | ABOUT HIVdb

Drug Resistance Interpretation: RT

NRTI Resistance Mutations:	None
NNRTI Resistance Mutations:	**K103N**
Other Mutations:	None

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	Susceptible
zidovudine (AZT)	Susceptible
emtricitabine (FTC)	Susceptible
lamivudine (3TC)	Susceptible
tenofovir (TDF)	Susceptible

Non-nucleoside Reverse Transcriptase Inhibitors	
doravirine (DOR)	Susceptible
efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	Susceptible
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	Susceptible

Key Questions: Individual Risk

- **HIVDR in persons with treatment failure**
  - Treatment failure could be defined as a single viral load elevation or two consecutive elevated measurements
  - If failing NNRTI-based
    - 60-90% have NNRTI resistance
    - 60-90% have m184V associated with 3TC/FTC resistance

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- **HIVDR in persons with treatment failure**
  - Treatment failure could be defined as a single viral load elevation or two consecutive elevated measurements
  - If failing NNRTI-based
    - 60-90% have NNRTI resistance
    - 60-90% have m184V associated with 3TC/FTC resistance
    - If failing TDF, K65R will be present in 20-60%

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NNRTI Resistance Mutations:	**K103N**
Other Mutations:	None

Nucleoside Reverse Transcriptase Inhibitors

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zidovudine (AZT)	Susceptible
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Intermediate Resistance

Non-nucleoside Reverse Transcriptase Inhibitors

doravirine (DOR)	Susceptible
efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	Susceptible
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	Susceptible

Key Questions: Individual Risk

- **HIVDR in persons with treatment failure**
  - Treatment failure could be defined as a single viral load elevation or two consecutive elevated measurements
  - If failing NNRTI-based
    - 60-90% have NNRTI resistance
    - 60-90% have m184V associated with 3TC/FTC resistance
    - If failing TDF, K65R will be present in 20-60%
    - If failing AZT, NRTI resistance to AZT will vary

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NNRTI Resistance Mutations:	**K103N**
Other Mutations:	None

Nucleoside Reverse Transcriptase Inhibitors

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Key Questions: Individual risk

- **HIVDR in patients failing PI-based therapy**
  - PI-resistance varies but usually not seen
  - NRTI-resistance more likely but may be from prior regimen failure
- **HIVDR in patients failing DTG-based therapy (more data needed)**
  - If ART-naive at time of initiation then HIVDR at failure extremely rare
  - If ART-experienced then risk of HIVDR appears low (at present)

Resistance testing interpretation: principles

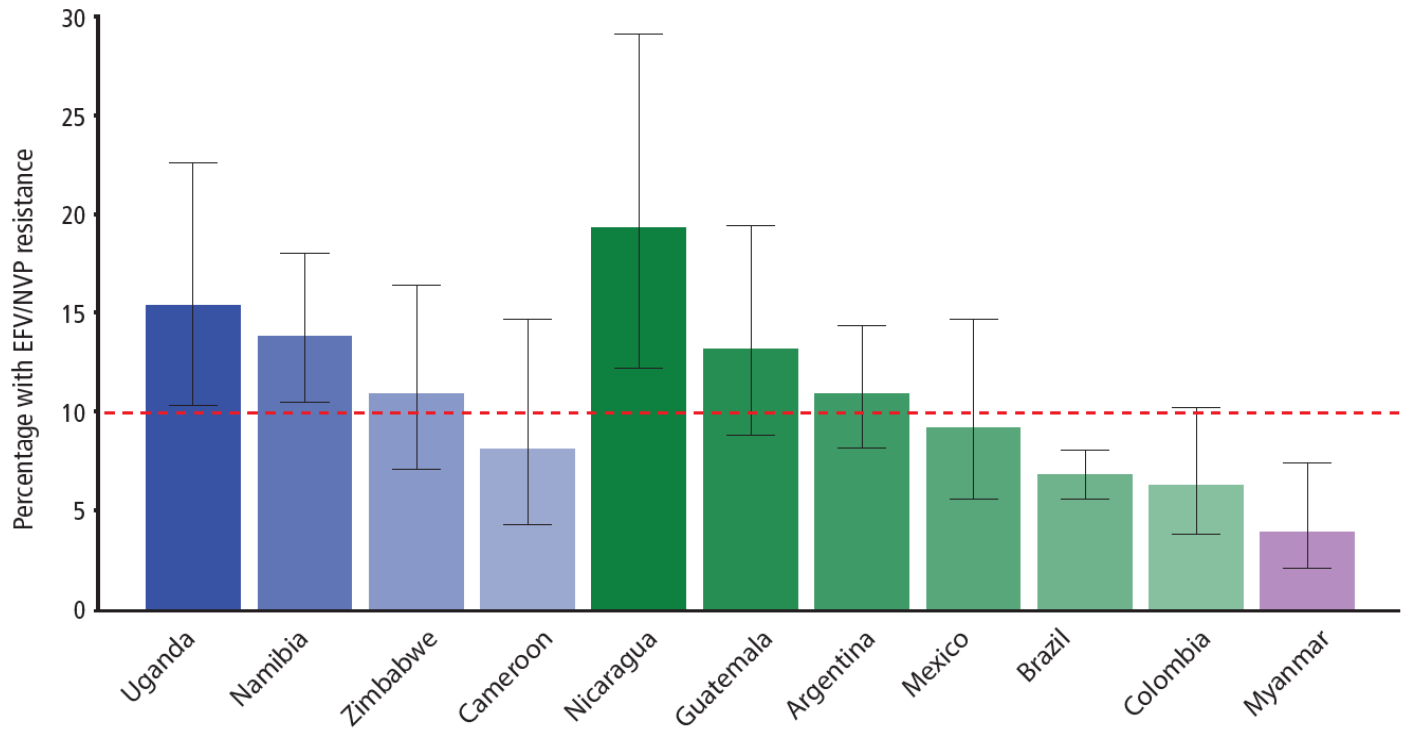
- Timing of resistance test key
  - Many DRMs wane with time and lack of ARV exposure
  - Ideal time is when patient is failing despite ongoing drug exposure
    - Often virologic failure associated with no drug intake
- Archived mutations may not be detected so need prior testing history (if available) or at minimum prior ARV exposure history
- Wild type (no DRMs detected):
  - Often associated with extreme non-adherence
  - Does not rule out archived resistance that will become apparent with drug exposure

Key Questions: Population Risk

- **Pre-treatment drug resistance (PDR):**
  - Reliant on surveillance (or sampling) of population initiating (or re-initiating) ART
  - Primarily focused on NNRTI resistance (greatest risk of treatment failure)
  - Risk of NNRTI PDR greater with prior ART exposure
  - Nationally representative surveys may not reflect prevalence of PDR in certain populations:
    - Pregnant women
    - Key populations such as FSWs, MSM
    - Urban vs. rural

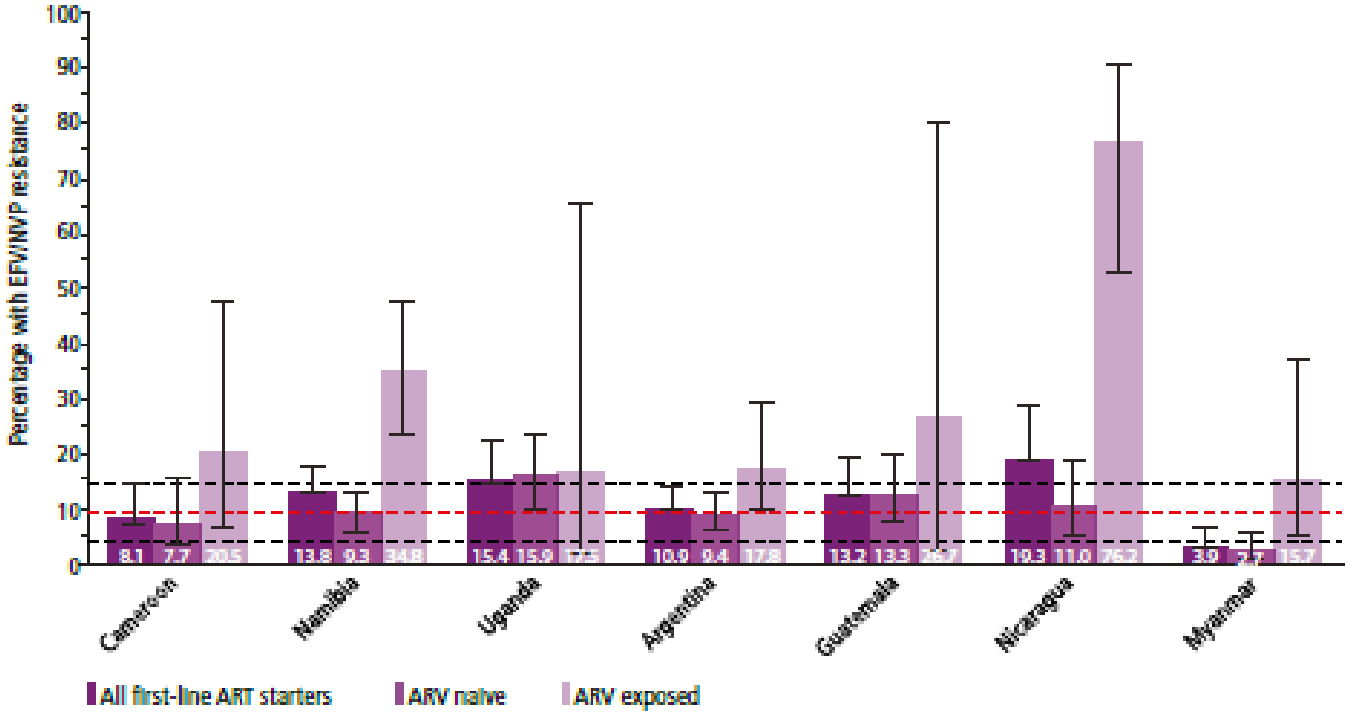
Drug resistance report (WHO 2017)

Fig. 3: **NNRTI (EFV/NVP) pretreatment HIV drug resistance**[11]



EFV= efavirenz; NVP= nevirapine.

Fig. 3.2. Resistance to EFV or NVP in first-line ART initiators by reported prior ARV drug exposure (national pretreatment HIVDR surveys, 2014–2016)



Resistance to EFV/NVP is defined by the Stanford HIVdb algorithm (version 8.3); sequences with predicted low-, intermediate- or high-level resistance are considered as resistant.

Source: *HIV drug resistance report 2017*. Geneva: World Health Organization; 2017 (1).

In Cameroon, PDR different in rural/urban settings

Table 2. Frequency of PDR

Variable	Overall	Urban sites	Rural sites
Total specimens eligible for genotyping, *n*	379	249	130
Total successfully genotyped, *n*	321	205	116
Genotyping rate, %	85	82	89
HIVDR in all initiators, *n*	321	205	116
any DRM, % (95% CI)	10.4 (5.4–19.1)	14.2 (6.6–27.9)	4.3 (1.2–14.3)
PI DRMs, % (95% CI)	0.3 (0.1–1.5)	0.5 (0.1–2.6)	0
NRTI DRMs, % (95% CI)	2.4 (0.4–12.9)	3.9 (0.6–20.9)	0
NNRTI DRMs, % (95% CI)	10.0 (5.1–18.8)	13.7 (6.2–27.5)	4.3 (1.2–14.3)
HIVDR in initiators with no prior exposure to ARVs	223	141	82
any DRM, % (95% CI)	10.4 (4.7–21.5)	13.5 (5.1–31.5)	5.3 (1.4–17.5)
PI DRMs, % (95% CI)	0.3 (0.0–2.1)	0.5 (0.1–3.7)	0
NRTI DRMs, % (95% CI)	2.8 (0.4–16.3)	4.6 (0.7–26.2)	0
NNRTI DRMs, % (95% CI)	10.1 (4.4–21.3)	13.1 (4.7–31.2)	5.3 (1.4–17.5)
HIVDR in initiators with prior exposure to ARVs, *n*	29	23	6
any DRM	14.7 (4.6–38.2)	18.8 (5.5–48.0)	0
PI DRMs	1.1 (0.1–8.8)	—	—
NRTI DRMs	1.6 (0.2–9.9)	—	—
NNRTI DRMs	13.6 (3.9–37.9)	—	—

—, not displayed.
Data are presented as *n*, % or study design-weighted proportion [% (95% CI)].

Tchouwa et al, Journal of Antimicrobial Therapy, Sept 2018

What does 10% NNRTI PDR (at the population) mean for an individual?

NNRTI PDR	VF at 12 months due to HIVDR (PDR X 0.75)	VF at 12 months due to other factors	VF at 12 months due to all factors	Proportion of VF due to PDR
5%	3.75%	10%	13.75%	27%
10%	7.5%	10%	17.5%	43%
15%	11.25%	10%	21.25%	53%
20%	15%	10%	25%	60%
30%	22.5%	10%	32.5%	69%

What does 10% NNRTI PDR (at the population) mean for an individual?

- **Most predictive models suggest 4-9 RR of VF with presence of NNRTI PDR**
  - Other factors also contribute to VF and not all studies show a statistically significant impact (ANRS 12249)
- **If viral load at 6 months is elevated should patients be switched to PI (or DTG)-based therapy?**

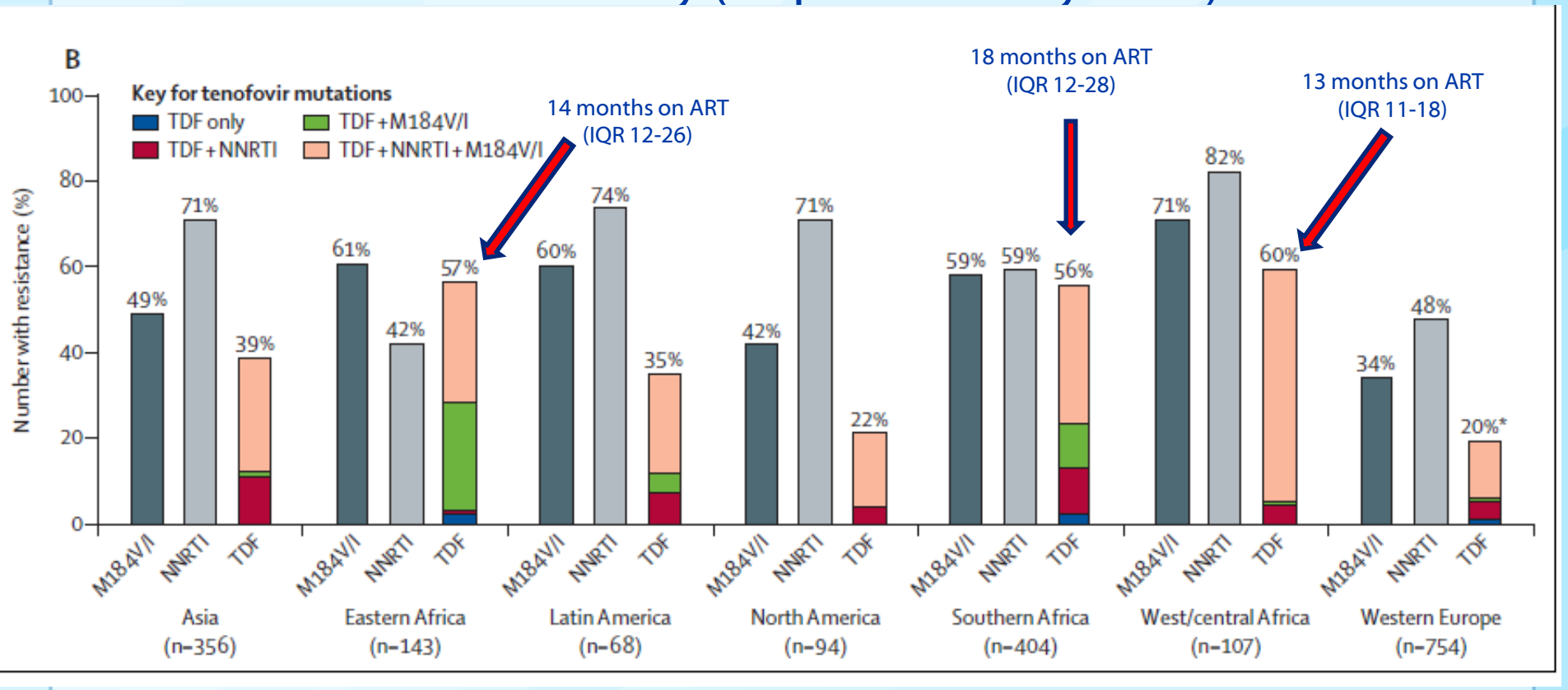
Key Questions: population-based risk of ADR

- **HIVDR patterns at 1st-line failure support guidelines for empiric 2nd-line ART**
- **Should NRTI component be switched?**
  - With 30-60% likelihood of K65R (TDF-resistant mutation)
  - Impact of loss of fixed-dose combination

TABLE 1. SUMMARY OF SEQUENCING OPTIONS FOR FIRST-, SECOND- AND THIRD-LINE ART REGIMENS FOR ADULTS (INCLUDING PREGNANT WOMEN AND ADOLESCENTS) AND CHILDREN

Population	First-line regimens	Second-line regimens	Third-line regimens
Adults and adolescents (including women and adolescent girls who are of childbearing potential or are pregnant)[a]	Two NRTIs + DTG[b]	Two NRTIs + (ATV/r or lopinavir/ritonavir (LPV/r))	Darunavir/ritonavir (DRV/r)[g,h] + DTG[i] + 1–2 NRTIs (if possible, consider optimization using genotyping)
	Two NRTIs + EFV[c]	Two NRTIs + DTG[b]	
Children	Two NRTIs + DTG	Two NRTIs + (ATV/r[d] or LPV/r)	
	Two NRTIs + LPV/r	Two NRTIs + DTG[e]	
	Two NRTIs + NNRTI	Two NRTIs + DTG[f]	

TenoRes Study (Gupta et al May 2016)



Prevalence of drug resistance by mutation and by region

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Children	Two NRTIs + DTG	Two NRTIs + (ATV/r[d] or LPV/r)	
	Two NRTIs + LPV/r	Two NRTIs + DTG[e]	
	Two NRTIs + NNRTI	Two NRTIs + DTG[f]	

HIVDR implications of transition to Dolutegravir-based regimens

- Rationale
  - Cost (TLD likely < TLE)
  - Better resistance profile
  - Less side effects
  - Capacity to produce up to 10 million bottles (30 day supply) per month will likely be achieved in 2018
- Over the next 3-5 years:
  - All adult and adolescent PLHIV initiating first-line regimens will be started on TLD (tenofovir/lamivudine/dolutegravir)
  - All adult and adolescent PLHIV on TLE or other alternate first line will be switched to TLD
    - Evidence of VL suppression prior to switch preferred
  - For consideration: All PLHIV on bPI-based 2nd-line ART will be switched to TLD
    - Alternate approach would be to substitute DTG for the bPI but only use TLD when switching from Tenofovir-based regimens

Potential public health threats of HIVDR in the TLD era

- Primary threat appears to be for DTG-resistance due to large populations receiving functional DTG monotherapy
  - Switched from TLE after resistance to NRTI components?
  - PrEP failures?
- Pre-treatment drug resistance threat much smaller though subsequent transmission of dolutegravir resistant virus following ADR a concern

HIVDR in sub Saharan Africa
Putting it all together

- Patients are failing ART
  - With documented elevated VL: acquired drug resistance likely though could be due to pre-existing drug resistance that was undetected
  - With unknown VL: failing at risk for further evolution of drug resistance though unlikely to impact response to standardized second-line ART

HIVDR in sub Saharan Africa
Putting it all together

- In the absence of access to individual drug resistance testing, surveillance systems and cohort data both needed to validate predictions of response to first and second-line ART
- Rollout of DTG is likely to mitigate the impact of HIVDR on treatment outcomes but systems and policies need to be in place that are prepared to signal early signs of resistance.

Questions?

For more information please contact Centers for Disease Control and Prevention

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