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EMERGENCE OF RESISTANCE TO DOLUTEGRAVIR IN THE REGION: THE NEED TO STRENGTHEN SURVEILLANCE

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Dr Phearavin Pheng, Head of Grant management office, University of Health and Science, Cambodia

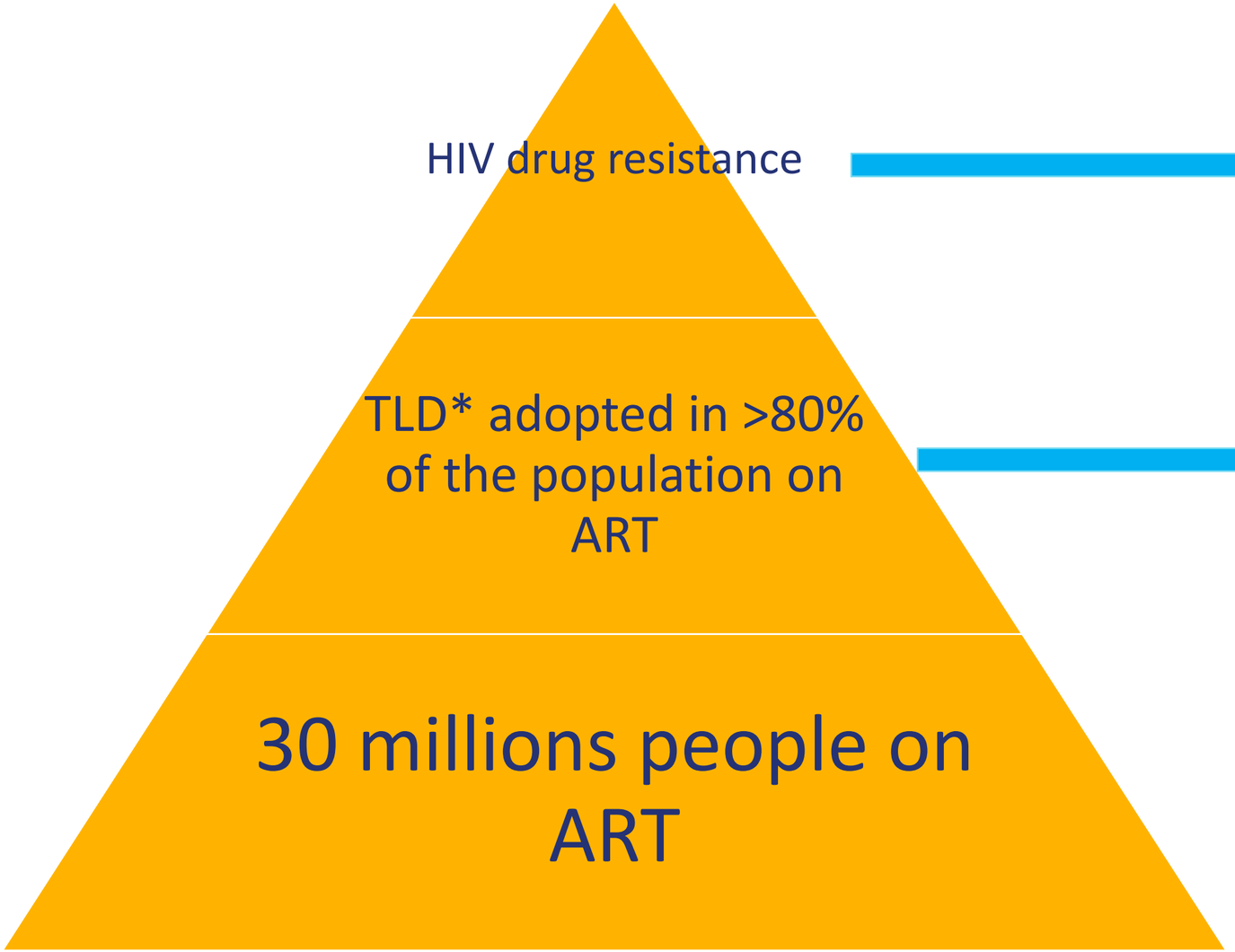
anrs MALADIES INFECTIEUSES ÉMERGENTES Inserm

OVERVIEW OF HIV DRUG RESISTANCE

3 drugs (Tenofovir-Lamivudine-Dolutégravir)=> 1 pill=> 0 :Undetectable HIV Viral Load = Untransmittable

U=U
UNDETECTABLE = UNTRANSMITTABLE

BACKGROUND ON ARV



Global Spread and Adoption of Dolutegravir:

- Since 2018, WHO has recommended use of DLT (dolutegravir) as the preferred first- and second-line HIV treatment for all population groups

- 2019 in Cambodia, 2020 in Vietnam

Over 116 /127 countries have adopted WHO's recommendation to use dolutegravir as the preferred first-line treatment.

* Tenofovir-Lamivudine-Dolutégravir

ARV

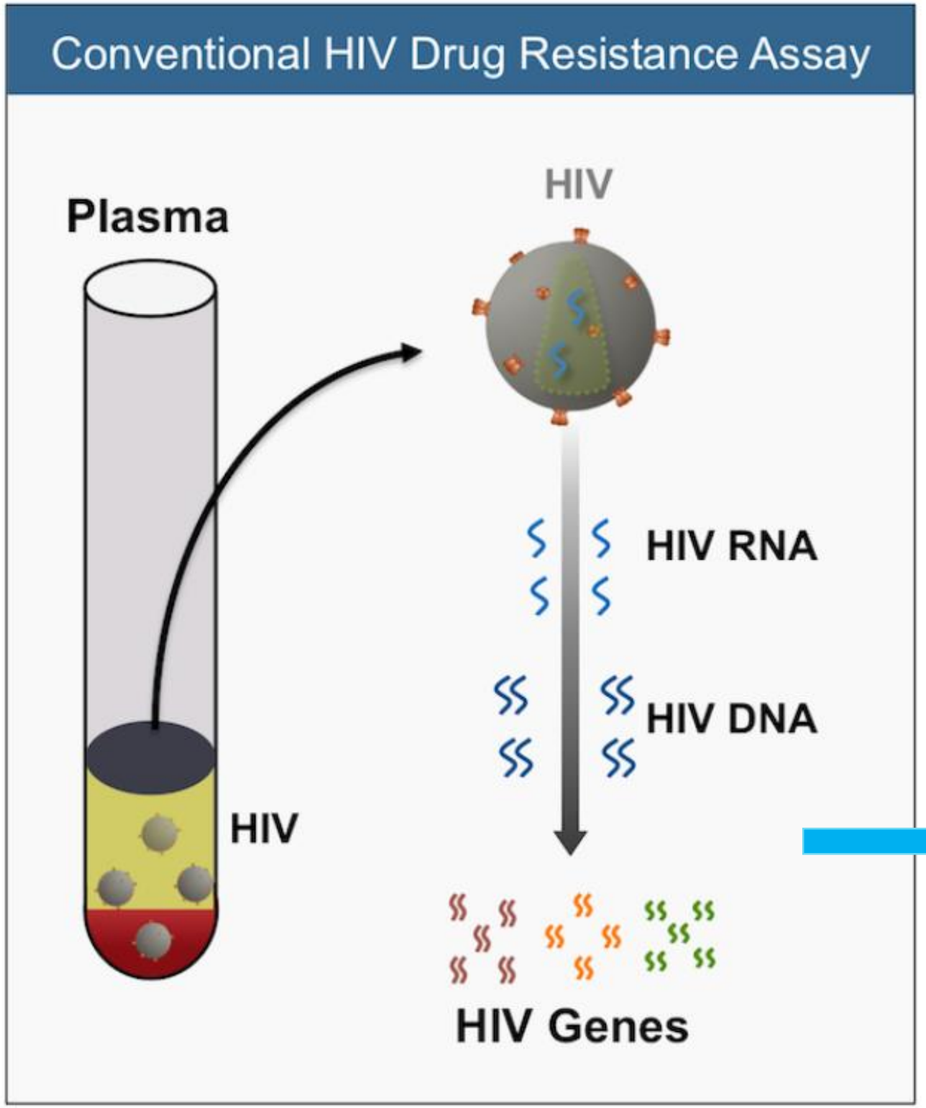
HIV drug resistance genotyping

-> PreTreatement

-> Drug failure

-> Mother to Child

In Cambodia second treatment failure



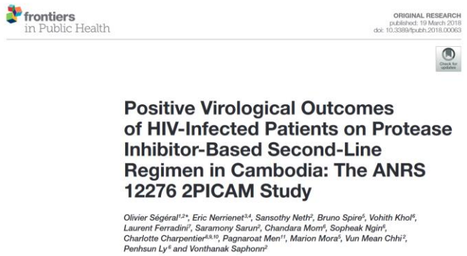
Mutations ?
Drug resistance

ANRS MIE – NCHADS ARV STUDIES IN CAMBODIA

1. Resistance on NNRTI in HIV patient occurred relatively quickly in patient with virological fealure

2. ANRS 12276 2PICAM study efficacy of Protease Inhibitor

3. ANRS 12374 3DICAM study Safety and efficacy of Darunavir/r and Dolutégravir on a 3-lign ARV regimen (under review Pheng P *et al.*)


frontiers in Public Health

ORIGINAL RESEARCH
published: 19 March 2018
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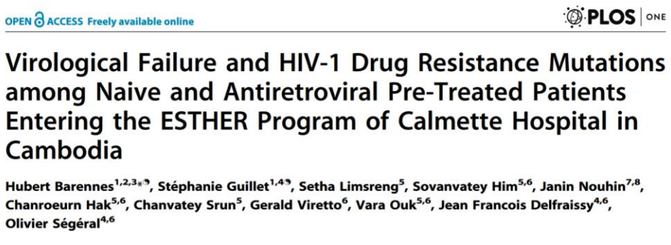
Positive Virological Outcomes of HIV-Infected Patients on Protease Inhibitor-Based Second-Line Regimen in Cambodia: The ANRS 12276 2PICAM Study

Olivier Ségéral[1,2*], Eric Nerrienet[3,4], Sansothy Neth[2], Bruno Spire[3], Vohith Khol[5], Laurent Ferradini[1], Saramony Sarun[2], Chandara Mom[2], Sopheak Ngin[5], Charlotte Charpentier[4,6,10], Pagnaroat Men[11], Marion Mora[5], Vun Mean Chhi[2], Penhsun Ly[4] and Vonthanak Saphonn[2]


OPEN ACCESS Freely available online

PLOS ONE

Virological Failure and HIV-1 Drug Resistance Mutations among Naive and Antiretroviral Pre-Treated Patients Entering the ESTHER Program of Calmette Hospital in Cambodia

Hubert Barennes[1,2,3]*, Stéphanie Guillet[1,4], Setha Limsreng[5], Sovanvatey Him[5,6], Janin Nouhin[7,8], Chanroeurn Hak[5,6], Chanvatey Srun[5], Gerald Viretto[6], Vara Ouk[5,6], Jean Francois Delfraissy[4,6], Olivier Ségéral[4,6]

DLT BREAKING NEWS

1. It is more effective
2. Easier to take
3. Has fewer side effects than other drugs currently in use*
4. It also has a high genetic barrier to developing drug resistance.

BUT

1. Among the four surveys reported, levels of resistance to dolutegravir ranged from 3.3% to 10,3%, and reached 22,6% among people experienced with treatment and switch to a DTG-containing ART while having high HIV viral loads.
2. To date, only a few countries have reported survey data to WHO.

MALAWI + ZAMBIE: Cohort 2 852 adults ARV -> switch to DLT, CV >400cc/ml after 2 years = 3,3%
DLT majors mutation = 2/45 with CV>1000 c/ml (4,4%)

LESOTHO: 15 299 patients INNTI switch to DLT, Genotying on 151 patient DLT majors mutation = 8/78 with CV>1000 c/ml (10,3%).

KENYA: 41 patient on first line. After 1,5 years of treatment CV> 200c/ml = 32%, DLT majors mutation =1/12 (8,3%)
190 Switch DLT from Pretreated patients (NNRTI or PI) After 2 years CV>200 = 28%, DLT majors mutation = 7/31 (22,6%)

NO DATA IN ASIA

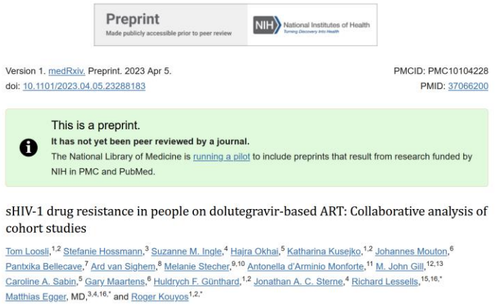
CROI 2024 abstracts 676, 187LB, 677,678

RISK FACTORS FOR RESISTANCE:

DLT

- The risk of developing DTG resistance is higher in individuals **with previous exposure to NNRTI-based regimens, poor adherence, and high viral loads at the time of switching to DTG-based ART.**

- **DTG monotherapy and dual therapy** with lamivudine (3TC) have been associated with a higher risk of resistance compared to combination ART with three or more drugs



Preprint
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National Institutes of Health

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This is a preprint.
It has not yet been peer reviewed by a journal.
The National Library of Medicine is running a pilot to include preprints that result from research funded by NIH in PMC and PubMed.

sHIV-1 drug resistance in people on dolutegravir-based ART: Collaborative analysis of cohort studies

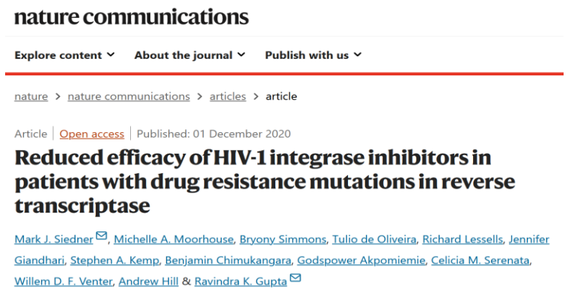
Tom Loosli,[1,2] Stefanie Hossmann,[3] Suzanne M. Ingle,[4] Haira Okhai,[5] Katharina Kusejko,[1,2] Johannes Mouton,[6] Pantxika Bellecave,[7] Ard van Sighem,[8] Melanie Stecher,[9,10] Antonella d'Arminio Monforte,[11] M. John Gill,[12,13] Caroline A. Sabin,[5] Gary Maartens,[6] Huldrych F. Günthard,[1,2] Jonathan A. C. Sterne,[4] Richard Lessells,[15,16,*] Matthias Egger, MD,[3,4,16,*] and Roger Kouyos[1,2,*]

PrEP

- The prevalence of pre-exposure prophylaxis (PrEP)-associated resistance (defined as resistance to tenofovir and/or lamivudine) is low for individuals who acquire HIV while receiving tenofovir-containing PrEP. However, the prevalence of tenofovir and or lamivudine resistance is more than 10-fold higher if PrEP is initiated during undiagnosed acute HIV infection.

IMPACT OF PRETREATMENT HIV DRUG RESISTANCE (PDR) ON DTG-BASED ART

- Pretreatment Drug Resistance (PDR) can significantly impact the effectiveness of dolutegravir (DTG)-based first-line antiretroviral therapy (ART).
- It can be either transmitted at the time of infection or acquired during previous treatments. The prevalence of PDR **varies by region** and can include resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) and nucleoside reverse transcriptase inhibitors (NRTIs).
- In some regions, such as sub-Saharan Africa, **the prevalence of NNRTI resistance is particularly high, which can complicate the effectiveness of DTG-based regimens**.
- The prevalence of DTG resistance varies significantly by region and country, with generally low levels in ART-naive populations but higher levels in treatment-experienced individuals, particularly in sub-Saharan Africa.


nature communications

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Article | Open access | Published: 01 December 2020

Reduced efficacy of HIV-1 integrase inhibitors in patients with drug resistance mutations in reverse transcriptase

Mark J. Siedner, Michelle A. Moorhouse, Bryony Simmons, Tulio de Oliveira, Richard Lessells, Jennifer Giandhari, Stephen A. Kemp, Benjamin Chimukangara, Godspower Akpomiemie, Celicia M. Serenata, Willem D. F. Venter, Andrew Hill & Ravindra K. Gupta


viruses MDPI

Article

Pre-Treatment HIV Drug Resistance and Genetic Diversity in Cameroon: Implications for First-Line Regimens

Joseph Fokam [1,2,3,4,*], Collins Ambe Chenwi [1,3,5,*], Valère Tala [1,3], Désiré Takou [1], Maria Mercedes Santoro [5], George Teto [1], Beatrice Dambaya [1], Felix Anubodem [1,3], Ezechiel Ngoufack Jagni Semengue [1,5,6], Grace Beloumou [1], Sandrine Djupsa [1], Edgar Assomo [1], Charles Fokunang [3], Claudia Alteri [7], Serge Billong [3,4], Nounouce Pamen Bouba [8], Rogers Ajeh [9], Vittorio Colizzi [1,5,6], Dora Mbanya [3,10,11], Francesca Ceccherini-Silberstein [5], Carlo-Federico Perno [1,12,†] and Alexis Ndjolo [1,3,†]

"The worrying evidence of resistance in individuals with unsuppressed viral load despite dolutegravir treatment underscores the necessity for increased vigilance and intensified efforts to optimize the quality of HIV care delivery,"
"**Standardized surveillance of HIV drug resistance is essential for effectively preventing, monitoring, and responding to these challenges**"

Dr Meg Doherty, Director, WHO Department of the Global HIV, Hepatitis and STI Programmes.

The emergence of acquired resistance to Dolutegravir (DTG) – the preferred antiretroviral drug – **may be higher than anticipated**, especially in people with heavy prior treatment experience.

Despite the emergence of resistance, DTG is a highly effective drug in HIV treatment, with more than 90% of patients achieving sustained viral suppression if adherent to treatment.

DTG resistance amplifies **the urgent need to implement standardized surveys to characterize the prevalence and patterns of DTG resistance mutations and their associated clinical determinants.**

TECHNICAL ASSISTANCE 2024 CAMBODIA

Programmatic Implications :

1. Monitoring and National Survey on PDR

2. to inform treatment guidelines and optimize patient outcomes.

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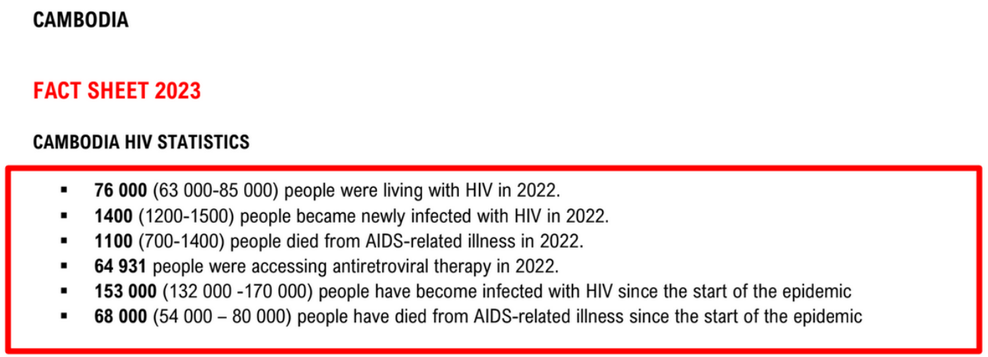
CAMBODIA NATIONAL PRETREATMENT HIV DRUG RESISTANCE SURVEYS AMONG ADULTS INITIATING DTG-BASED FIRST-LINE ART (SO1)

Progress as of June 2024

SURVEY BACKGROUNDS



CAMBODIA

FACT SHEET 2023

CAMBODIA HIV STATISTICS

- **76 000** (63 000-85 000) people were living with HIV in 2022.
- **1400** (1200-1500) people became newly infected with HIV in 2022.
- **1100** (700-1400) people died from AIDS-related illness in 2022.
- **64 931** people were accessing antiretroviral therapy in 2022.
- **153 000** (132 000 -170 000) people have become infected with HIV since the start of the epidemic
- **68 000** (54 000 – 80 000) people have died from AIDS-related illness since the start of the epidemic

- In Cambodia, DTG-based first-line and second-line regimens have been widely implemented since 2019.
- By Q3 2022, **39,242**/64 900 PLHIV had started the **DTG first-line regimen**.
- **But data** on pretreatment drug resistance (PDR) and acquired drug resistance (ADR) in patients failing DTG-based regimens **are unavailable**.
- PDR can significantly impact the effectiveness of DTG-based first-line ART by increasing the risk of virological failure and the emergence of drug resistance. This underscores the importance of routine resistance testing, and **timely regimen adjustments to ensure the long-term success of DTG-based therapies**.

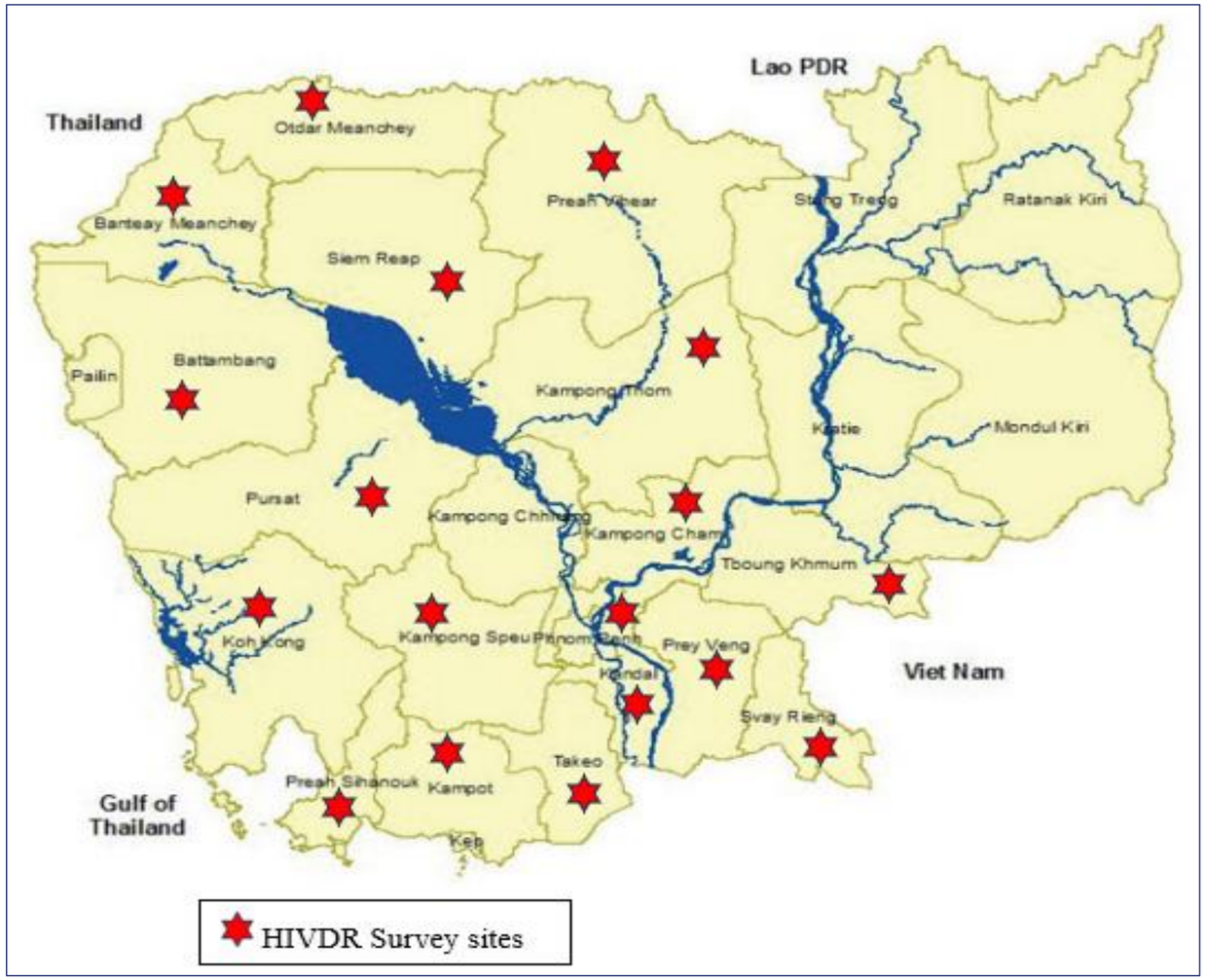
- WHO recommends routine surveillance of HIV drug resistance to inform treatment guidelines and optimize patient outcomes.

SURVEY OVERVIEW

- **The purpose of this survey:**
  - To estimate a nationally prevalence of HIVDR among **all ART initiators** and among **initiators without prior exposure to ARV drugs** in Cambodia.

- **Methods:**
  - Design: Cross-sectional survey using a two-stage cluster design
  - Inclusion criteria:
    - Adults: defined as aged +15yrs old and above with HIV-1/2 infection who could legally provide informed consent.
    - All individuals initiating ART (including as first-line treatment of their own health or PMTCT for the first time or for reinitiating if they have stopped for more than three months.
  - Exclusion criteria:
    - Patients transferred-in already receiving ART as well as those who interrupted their ART for less than 3 months.
  - **Sample size and Sampling:**
    - Sample size: **317**, 45 clusters (ART clinics) in 23 provinces selected via PPS.
    - **7 patients per cluster/ART clinic** will be selected using a consecutive sampling method.

GEOGRAPHICAL DISTRIBUTION OF THE HIV DRUG RESISTANCE SURVEY SITES ACROSS CAMBODIA



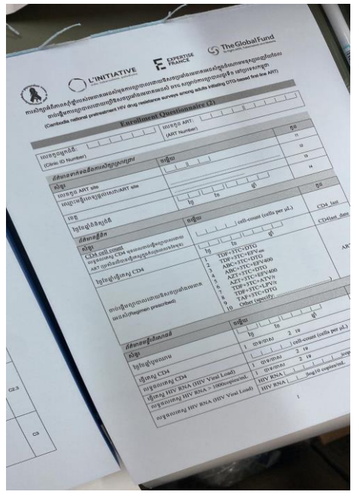
SURVEY SAMPLE PROCESSING FLOWCHART

Inclusion
ART Clinics

→ Samples sent to Reference Laboratory regional (CD4/Virad Load)

→ Centralized NCHADS Laboratory (CD4/Viral Load)

→ Samples sent to IPC* Laboratory (GRT)



***IPC: Institute Pasteur In Cambodia**

PROGRESS AS OF JUNE, 2024

- NECHR approval: November 02, 2024
- Data collection training: November 07-12, 2024
- Recruitement started: Mid Jan, 2024, Suspended due to funnding gap: End of Jan 2024. Resumed End of March, 2024 (27/03/2024).
- **9/32 sites** started the patients recruitments
  - 2 sites completed the recruitments: Chhouksar and NCHADS/AHF clinic 3.
  - 5 sites did not received the survey kits yet.
- **101/317 patients recruited.**
- **Xx/ 101 samples received at NCHADS Lab**
- **xx/101 samples transferred to IPC for GRT**
- **46/101 results sent back to sites (CD4, VL, GRT)**

MAIN CHALLENGES IN CONDUCTING HIV PDR SURVEYS

- **Geographical and Logistical Barriers:** Remote and rural areas may face logistical challenges in sample collection and transportation, which can delay or hinder the implementation of PDR surveys.

- **Resource Limitations:** Conducting PDR surveys requires significant financial and technical resources, which may not be readily available in low- and middle-income countries. This includes the costs of genotyping, laboratory infrastructure, and trained personnel.

- **Data Collection and Standardization:** Ensuring consistent and standardized data collection across different regions and countries can be challenging. Variability in survey methods, sample sizes, and data reporting can affect the comparability and reliability of the results

- **Access to Testing:** In many regions, especially in low-income countries, access to genotypic resistance testing is limited. This is often due to the lack of laboratory facilities and the high costs associated with testing.

NEXT STEPS

1. Check and collect the questionnaires of the patients enrolled (101 patients) from the survey sites.

2. Plan a meeting end of June 2024 to review the progress of the screening and recruitment at each sites and make a decision to realocate the number of recruitment to the biguest sites.

3. Expected date to start the data cleaning and analysis: August 2024.

4. Monitoring plan of PDR for PLHIV in Cambodia

GLOBAL HIV TREATMENT NEXT CHALLENGES

1. DLT transition : - Resistance monitoring
- Side Effects (Weight)
- others combinations

2. Viral Load access : expand Point of Care, increase capacities of laboratories

3. Service delivery : Continued focus on a patient-centered view, more integrated care with other services (includind TB, NCDs Mental Health and HPV screening)

→ - ANRS ELDORADO Study DLT vs Doravirine
- Use dual regiments (eg: DTL/3TC) and long acting combinations still need further clinical studies in the context of LMICs

→ HPV screening on women living with HIV in Cambodia
- ANRS AIMA CC study (paper on press)
- Ongoing Initiative Technical Assitance