# HIV : Global Implications of the Philippine Epidemic

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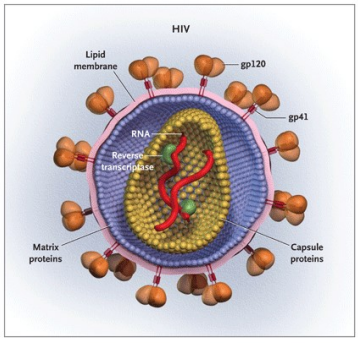
## Objectives

1. To give an update on the HIV epidemic in the Philippines and its clinical and molecular epidemiology and its implications on the global epidemic
2. To discuss current research on prevalence, response to treatment and emerging drug resistance
3. To discuss how results from our research studies have translated into action, and how it will inform how we respond to the epidemic

## HIV

- Human Immunodeficiency Virus
- Causative agent of Acquired Immune Deficiency Syndrome
- RNA virus – retrovirus, uses reverse transcriptase enzyme
- Target Cell is T-helper ($CD_4$/CCR5 positive cells)
- Causes unregulated immune activation leading to collapse

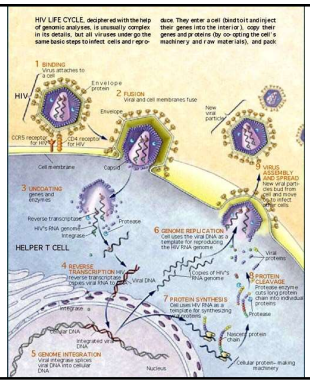



Johnson and Fauci, NEJM 2001;345:1015 Figure 1

## Selective Timeline of HIV/AIDS

- 1981 – 1st cases of PCP, KS reported
- 1983 – Retrovirus isolated and identified
- 1985 – Blood supply testing began (EIA)
- 1987 – Azidothymidine (ZDV) approved
- 1987-1995 – Dual-NRTI regimens
- 1992 – PCP Prophylaxis: better outcomes[1]
- 1995 – CCR5 identified as 1° receptor
- 1996 –HAART era began: Introduction of PIs

Chaisson RE et al. *Arch Intern Med*. 1992 Oct; 152(10):2009-13.




http://virusbioinformatics.org/image/HIV_virus_life_cycle.jpg

## How does HIV cause AIDS?

- Early infection depletes most gut associated $CD_4$ cells
- During the latent phase, viremia is at a low level, but there is evidence that ongoing viral replication causes unregulated immune stimulation
- Constant immune stimulation eventually leads to immune dysregulation and destruction of $CD_4$ cells

## CD4 + cell

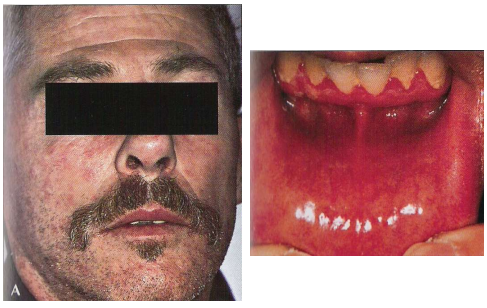
- Mostly T-helper cells, also found in some histiocytes including Langhans cells and reticuloendothelial cells which serve as reservoir sites
- $CD_4$+ T-cell is the lynchpin of cellular-mediated immune system

## CCR5 and CXCR4

- Primary receptor of HIV found to be $CCR_5$, and not $CD_4$
- $\Delta_{32}$ mutation confer high level protection against infection with $CCR_5$ virus
- $CCR_5$ and $CXCR_4$ are chemokine receptors, $R_4$ is essential to life
- Emergence of $R_4$ viruses might be a late phenomonon in disease

## Natural history

- Acute HIV infection is characterized by a flu-like illness with lymphadenopathy, fever and malaise
- Self-limited and patient usually recovers
- Takes 8 to 10 years to develop AIDS



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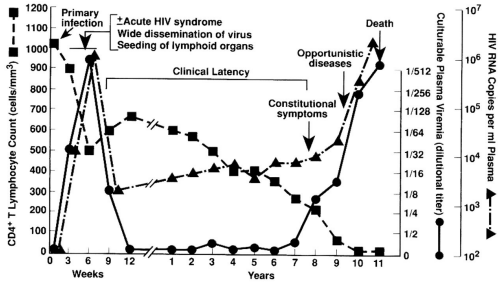



From Fauci AS, Pantaleo G, Stanley S, Weissman D. Immunopathogenic mechanisms of HIV infection. Ann Intern Med. 1996 Apr 1;124(7):654-63.

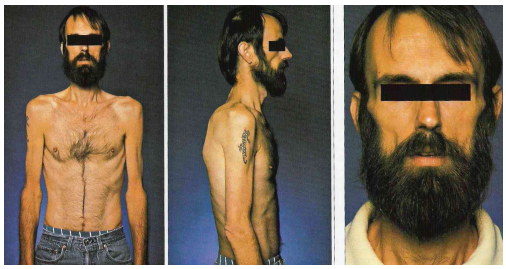
## AIDS

- Defined either by laboratory parameters in an asymptomatic patient, or by an AIDS-defining illness, usually an opportunistic infection
- $CD_4$ < 200 is AIDS
- Opportunistic infections: PCP, MAC, *Cryptococcus* meningitis, Kaposi's sarcoma, CNS lymphoma, esophageal thrush etc. = AIDS at **ANY** $CD_4$ count

| Rank | OI | Cases | %Prevalence N=476 | % of OIs n=155 | CD4 Mean (cells/mL) | Range (cells/mL) | CD4 Median (cells/mL) | 95% CI (cells/mL) | Deaths | Mortality |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | PTB | 73 | 15.3 | 47.1 | 161 | 1-663 | 88 | 118-203 | 5 | 6.8 |
| 2 | PCP | 50 | 10.5 | 32.3 | 86 | 1-576 | 34 | 51-121 | 4 | 8 |
| 3 | ePTB | 27 | 5.7 | 17.4 | 160 | 2-429 | 135 | 93-227 | 0 | 0 |
| 4 | dis TB | 11 | 2.3 | 7.1 | 30 | 2-164 | 30 | 14-108 | 1 | 9.1 |
| 5 | othrush | 11 | 2.3 | 7.1 | 136 | 2-347 | 104 | 54-218 | 1 | 9.1 |
| 6 | CMV | 9 | 1.9 | 5.8 | 48 | 3-189 | 6 | 0-111 | 1 | 11.1 |
| 7 | crypto | 6 | 1.3 | 3.9 | 35 | 24-49 | 35 | 21-49 | 1 | 16.7 |
| 8 | ethrush | 5 | 1.1 | 3.2 | 64 | 6-218 | 16 | 0-165 | 0 | 0 |
| 9 | toxo | 3 | 0.6 | 1.9 | 13 | 11-15 | 12 | 10-15 | 0 | 0 |

**Table 1.** OIs and associated characteristics (Salvana et al., ID Week 2012)
Legend: OI - opportunistic infection PTB - pulmonary tuberculosis; PCP - *Pneumocystis* pneumonia; ePTB - extrapulmonary tuberculosis; dis TB - disseminated tuberculosis; othrush - oral thrush; CMV - cytomegalovirus; crypto - *Cryptococcus* meningitis; ethrush - esophageal thrush; toxo - toxoplasmosis

AIDS wasting syndrome



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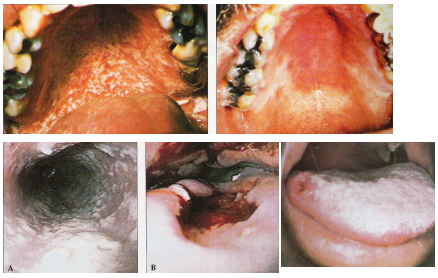

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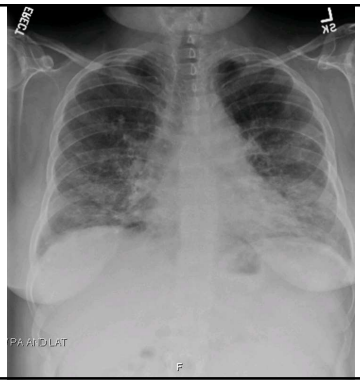
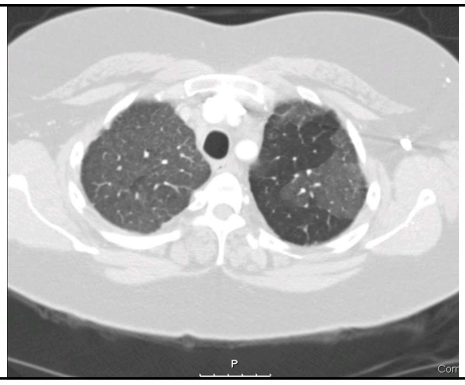
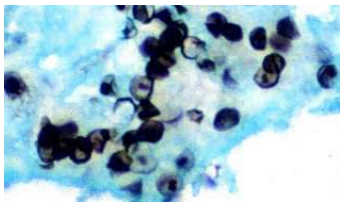
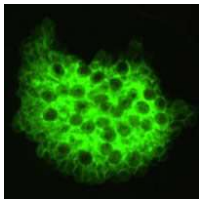
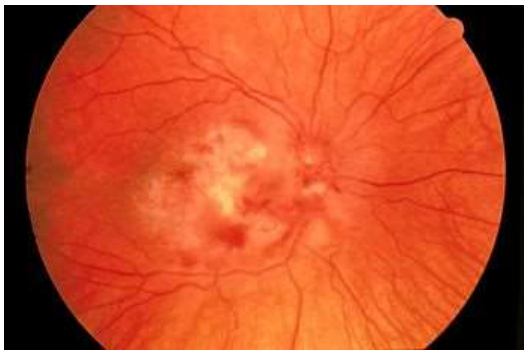
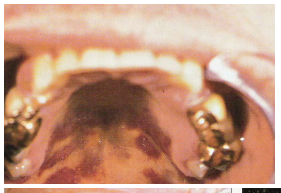
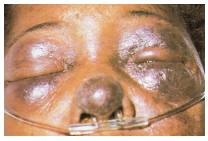
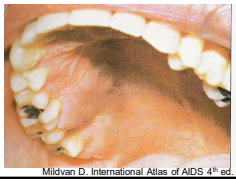
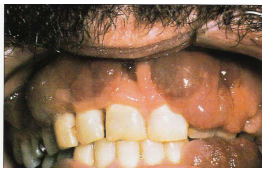


http://www.dpd.cdc.gov/dpdx/HTML/Pneumocystis.htm



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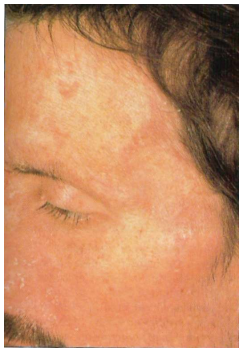

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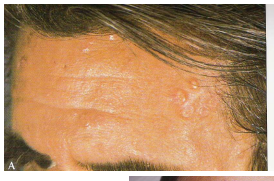
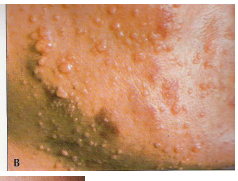

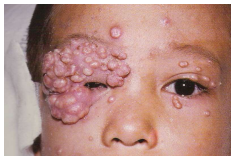

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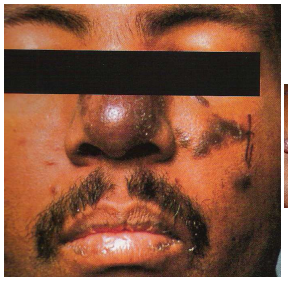
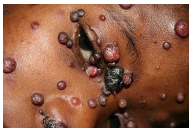

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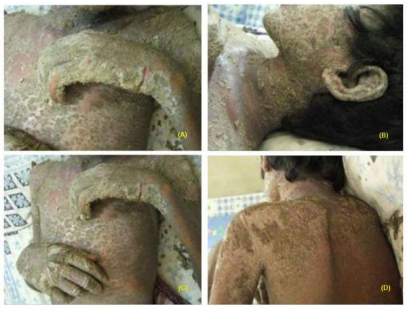
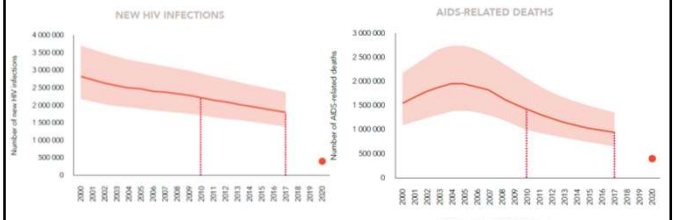


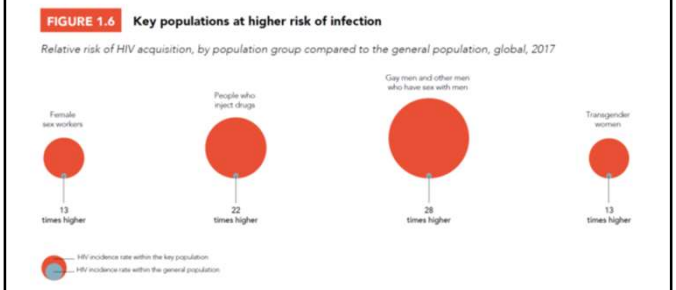
Ramachandran et al. 2008
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2276223/

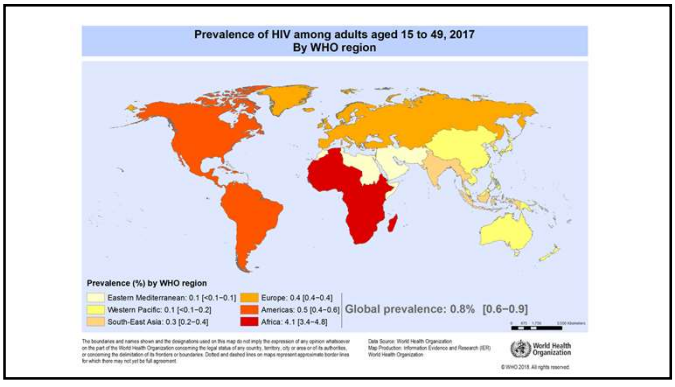
## Epidemiology

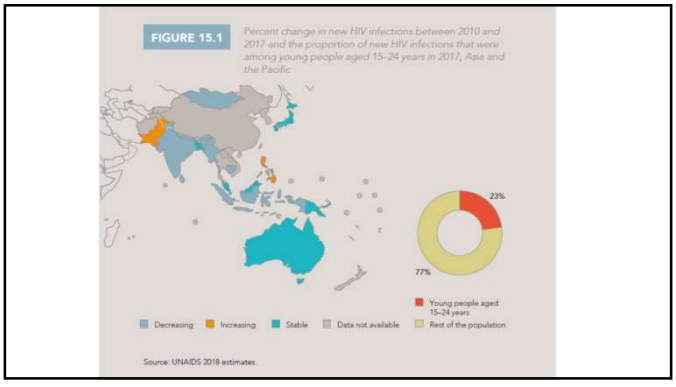
- 36.9 million people worldwide are currently living with HIV
- 36 million have previously died from AIDS
- 1.8 million new cases in 2017
- 940,000 deaths reported
- number of new cases has declined by 18% since 2010
- number of deaths has decreased by 34% since 2010
- 21.7 million on treatment

UNAIDS, 2018



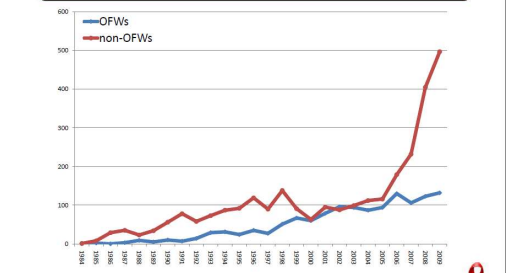
*Trends in new HIV infections among adults (aged 15 years and older), by country, 2010–2017*

| | |
|---|---|
| **Decrease of 50% or more** | Cambodia, Mongolia*, Nepal. |
| **Decrease of 25– <50%** | Armenia, Austria, Bahamas, Eswatini, France, Kenya, Kyrgyzstan, Malawi, Mauritania, Myanmar, Netherlands, Portugal, Sierra Leone, South Africa, Trinidad and Tobago, Uganda, Zimbabwe. |
| **Decrease of 5– <25%** | Albania*, Barbados, Bulgaria, Cameroon, Central African Republic, Cuba, Democratic Republic of the Congo, Denmark, Dominican Republic, El Salvador, Estonia, Gambia, Georgia, Guatemala, Guinea-Bissau, Guyana, Haiti, Indonesia, Iran (Islamic Republic of), Jamaica, Lesotho, Morocco, Mozambique, Namibia, Nicaragua, Niger, Norway, Peru, Romania, Rwanda, Senegal, Serbia, Singapore, Somalia, Spain, Sri Lanka, Togo, Ukraine, United Republic of Tanzania, Uruguay, Zambia. |
| **Change of +/- <5%** | Angola, Bolivia, Brazil, Chad, Comoros*, Ecuador, Gabon, Ghana, Guinea, Italy, Japan, Nigeria, Paraguay, Republic of Moldova, South Sudan, Tajikistan. |

| | |
|---|---|
| **Increase of 5– <25%** | Argentina, Australia, Azerbaijan, Bahrain*, Bangladesh, Belize, Benin, Botswana, Cape Verde, Congo, Côte d'Ivoire, Djibouti, Equatorial Guinea, Honduras, Liberia, Malaysia, Mali, Mexico, Panama, Papua, New Guinea, Slovenia*, Sudan, Tunisia. |
| **Increase of 25– <49%** | Algeria, Belarus, Burkina Faso, Burundi, Costa Rica, Cyprus*, Eritrea, Ethiopia, Greece, Luxembourg*, Pakistan, Russian Federation, Suriname. |
| **Increase of 50% or more** | Chile, Czech Republic, Egypt, Hungary, Lithuania, Kazakhstan, Kuwait*, Madagascar, Montenegro*, Philippines, Qatar*, Slovakia, The former Yugoslav Republic of Macedonia*, Uzbekistan. |

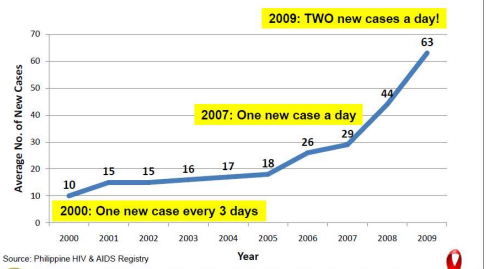
* Countries with fewer than 100 new infections in the adult population.
Source: UNAIDS 2018 estimates.

## OFWs vs Non-OFWs




THIS IS IT! NEC TALKS ON HIV

## Average Number of Cases per Month




THIS IS IT! NEC TALKS ON HIV

- June 2018: 993 cases
- **31 new cases/day**
- Reached 10,000 cases for the first time in history last year

## 31 cases/day

- Contrast: 1 new case every day in 2007
- **31-fold increase** in the last decade
- 56,275 confirmed cases since 1984
- **Nearly 85% newly diagnosed in the last five years**

## New Cases From 2010-2017

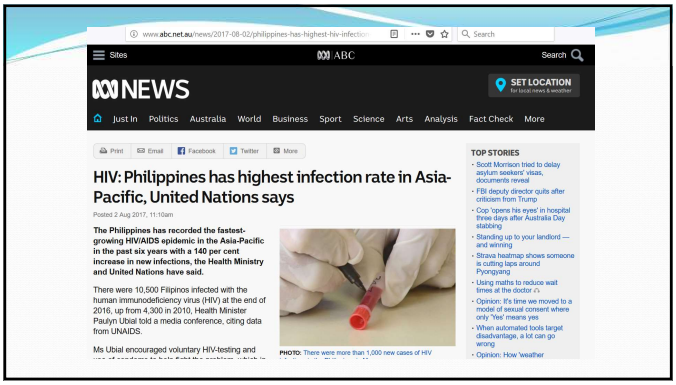
18% ↓ WORLD

6013% ↑ PHILIPPINES


**Table 3. Modes of HIV transmission**

| Mode of Transmission | Jun 2018 (N=993) | | Jan–Jun 2018 (N=5,673) | | Jan 2013-Jun 2018 (N=44,603) | | Jan 1984-Jun 2018 (N=56,275)[3] | |
|---|---|---|---|---|---|---|---|---|
| | M[2] | F[3] | M | F | M | F | M | F |
| Sexual contact | 922 | 55 | 5,237 | 294 | 40,866 | 1,897 | 50,183 | 3,355 |
| *Male-female sex* | 61 | 55 | 457 | 294 | 4,049 | 1,897 | 5,941 | 3,355 |
| *Male-male sex* | 594 | - | 3,321 | - | 23,430 | - | 27,989 | - |
| *Sex w/ males & females*[1] | 267 | - | 1,459 | - | 13,387 | - | 16,253 | - |
| Blood/blood products | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 15 |
| Sharing of needles | 5 | 2 | 91 | 6 | 1,566 | 78 | 1,965 | 119 |
| Needlestick injury | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 |
| Mother to child | 0 | 2 | 6 | 4 | 53 | 41 | 84 | 69 |
| No data | 7 | 0 | 35 | 0 | 96 | 6 | 383 | 83 |

[2] Sex at birth; M= Male, F = Female
[3] No data on sex for 11 cases
[1] Among males only




## Why now?

- 92.5% circumcision rate in Filipinos
- Increased local transmission
- Increased MSM transmission
- new strains – recent data from our lab shows major shift from subtype B to CRF01_AE – more aggressive Thai strain
- ?better testing
- Lowest condom use in Asia: 30%

## Origin of HIV

- traced to a simian virus, SIVcpz from chimpanzees
- likely bloodborne transmission to human hunters
- Phylogenetic analysis points to at least five different independent transmission events in the 20th century

- HIV-1: major (M, between 1915 and 1941), outlier (O), and nonmajor and nonoutlier (N)
- earliest documented case of HIV-1 infection (with group M strain) blood sample from 1959 in Kinshasa, Zaire
- O may be from gorillas
- Newly described P from gorillas
- BUT gorillas got it from the Chimps!
- HIV-2 Sooty Mangabeys

## Classification and Molecular Epidemiology of HIV

- Group M the predominant circulating HIV-1 group
- M subtypes, denoted with letters, and sub-subtypes, denoted with numerals.
- Subtypes A1, A2, A3, A4, B, C, D, F1, F2, G, H, J, and K are currently recognized.

## CRF's and URF's

- advances in full-genome sequencing of HIV have led to the identification of circulating and unique recombinant forms
- result of recombination between subtypes within a dually infected person, from whom the recombinant forms are then passed to other people
- classified as circulating recombinant forms if they are identified in three or more people with no direct epidemiologic linkage; otherwise they are described as unique recombinant forms

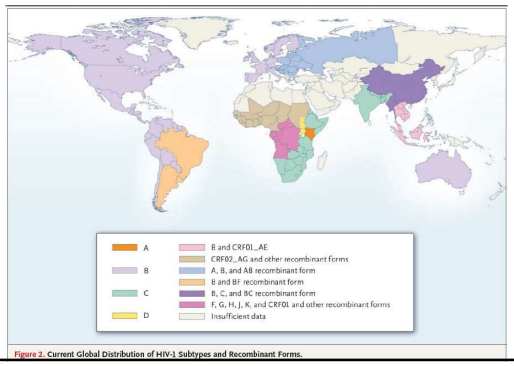


Figure 2. Current Global Distribution of HIV-1 Subtypes and Recombinant Forms.

Table 2. Features of the HIV-1 Pandemic, According to Subtype or Circulating Recombinant Form (CRF).*

| Subtype or CRF | Location | Global Prevalence | Tropism and Replication | Disease Progression | Response to Therapy |
|---|---|---|---|---|---|
| **Subtype** | | | | | |
| A | East and Central Africa, Central Asia, Eastern Europe | 12.3% | Mostly uses CCR5, even in late infection[60] | NA | No significant difference as compared with C and D[24] |
| B | Americas, Western Europe, East Asia, Oceania | 10.2% | Uses CCR5 early, with increasing use of CXCR4 in late infection[58] | HLA-B7 associated with poor CTL response and increased viremia[61,62]; HLA-B57 associated with slow progression[63]; B strain in Brazil associated with slow progression[64] | NA |
| C | India, Eastern and Southern Africa | 49.9% | Mostly uses CCR5, even in late infection[58]; increased vaginal shedding[59] and mother-to-child transmission[59,65] | HLA-B57 associated with slow progression[63] | No significant difference as compared with A and D[24]; differential pathways to resistance[66–69] |
| D | East Africa | 2.5% | Uses CXCR4 in early infection[27] | Progression more rapid than A in Uganda, Kenya, and Tanzania[57,70] | NA |
| G | West Africa | 6.3% | NA | NA | NA |
| F, H, J, and K | Various | Each <1.0% | NA | NA | NA |
| **CRF** | | | | | |
| CRF01_AE | Southeast Asia | 4.7% | May have higher initial viral load than B but subtype may be a confounder[71] | Possibly accelerated progression as compared with B[66] | NA |
| CRF02_AG | West Africa | 4.8% | Higher rate of replication in vitro than B[53] | NA | NA |
| Other | Various | Each <0.1% | NA | NA | NA |

* Location and prevalence data are from Hemelaar et al.[10] Other CRFs include CRF03 through CRF43, and this category is expanding. CTL denotes cytotoxic T lymphocyte, and NA not available.

## Response to Therapy

- only 12% of global infections are caused by the most studied subtype, B; and 50% of prevalent HIV infections and 47% of all new HIV-1 infections are with subtype C
- discrepancy in the availability of clinical data for non-B subtypes is exacerbated by the fact that, until the past few years, antiretroviral treatment had been largely unavailable in many countries with non-B subtypes of HIV-1

- certain subtypes of HIV-1 might spread or progress more rapidly than others, making treatment decisions more challenging
- data on baseline antiretroviral susceptibility derived from studies of subtype B may not be applicable to non-B subtypes

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The changing molecular epidemiology of HIV in the Philippines

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ABSTRACT

*Background:* The Philippines has one of the fastest-growing HIV epidemics in the world. Possible reasons for this include increased testing, increased local transmission, and possibly more aggressive strains of HIV. This study sought to determine whether local molecular subtypes of HIV have changed.
*Methods:* Viruses from 81 newly diagnosed, treatment-naive HIV patients were genotyped using protease and reverse transcriptase genes. Demographic characteristics and CD4 count data were collected.
*Results:* The cohort had an average age of 29 years (range 19–51 years), CD4+ count of 255 cells/mm$^3$ (range 2–744 cells/mm$^3$), and self-reported acquisition time of 2.42 years (range 0.17–8.17 years). All were male, including 79 men who have sex with men (MSM). The genotype distribution was 77% CRF01_AE, 22% B, and 1% C. Previous data from 1985–2000 showed that most Philippine HIV infections were caused by subtype B (71%, $n = 100$), followed by subtype CRF01_AE (20%). Comparison with the present cohort showed a significant shift in subtype ($p < 0.0001$). Comparison between CRF01_AE and B showed a lower CD4+ count (230 vs. 350 cells/mm$^3$, $p = 0.03$). Survival data showed highly significant survival associated with antiretroviral (ARV) treatment ($p < 0.0001$), but no significant difference in mortality or CD4 count increase on ARVs between subtypes.
*Conclusions:* The molecular epidemiology of HIV in the Philippines has changed, with the more aggressive CRF01_AE now being the predominant subtype.


## Analysis

- CRF01_AE (75%), B (22%), C (1%) and CRF01_AE/K (1%) (N=81)
- 1985-2000 (pooled) subtype B (71%, N=100), followed by subtype CRF01_AE (20%)
- **Major Genotype Shift (P<0.001)**
- Cohort baseline demographics:
  Age: 29 estimated Time of acquisition: 2.4 years
  CD4 count: 254 cells/μL
- **CD4 count of CRF01 AE significantly lower at presentation versus B (233 versus 350, p=0.03)** despite no difference in age (p=0.15) and time to acquisition (p=0.66)

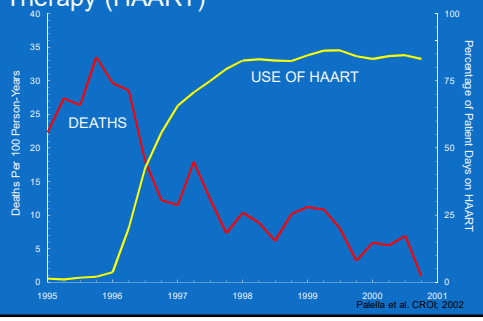
## Global Implications

- AE and other non-B type infections are emerging in other countries including US, Canada, Australia
- Secondary epidemic may occur, just like explosive epidemic in the Philippines with genotype shift
- This may also be coupled with rapid emergence of drug resistance


## From death sentence to chronic disease

- After an unprecedented global effort in research and aid, effective medication was discovered
- Turning point came with discovery of protease inhibitors, and use of HAART

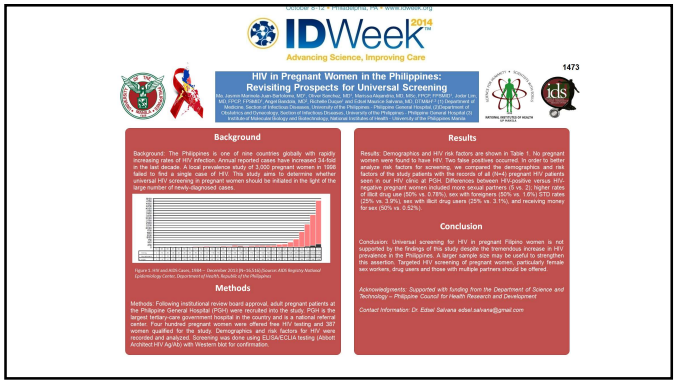
## Mortality and Highly Active Antiretroviral Therapy (HAART)




Palella et al. CROI 2002

## Who to test in practice?

- Anyone with risk factors = **anyone who is sexually active!**
- Occupational risk – healthcare workers with needle sticks and blood borne pathogen exposure
- Cost effective to test if prevalence in a particular population is >0.1%
- Yes MSM, FSW, IVDU
- What about pregnant women, cervical cancer, TB, STI patients?



IDWeek 2014
Advancing Science, Improving Care

**HIV in Pregnant Women in the Philippines: Revisiting Prospects for Universal Screening**

1473

**Background**

Background: The Philippines is one of nine countries globally with rapidly increasing rates of HIV infection. Annual reported cases have increased 34-fold in the last decade. A local prevalence study of 3,000 pregnant women in 1998 failed to find a single case of HIV. This study aims to determine whether universal HIV screening in pregnant women should be initiated in the light of the large number of newly diagnosed cases.

**Methods**

Methods: Following institutional review board approval, adult pregnant patients at the Philippine General Hospital (PGH) were recruited into the study. PGH is the largest tertiary-care government hospital in the country and is a national referral center. Four hundred pregnant women were offered free HIV testing and 397 women qualified for the study. Demographics and risk factors for HIV were recorded and analyzed. Screening was done using ELISA/ECLIA testing (Abbott Architect HIV Ag/Ab) with Western blot for confirmation.

**Results**

Results: Demographics and HIV risk factors are shown in Table 1. No pregnant women were found to have HIV. Two false positives occurred. In order to better analyze risk factors for screening, we compared the demographics and risk factors of the study patients with the records of all (N=6) pregnant HIV patients seen in our HIV clinic at PGH. Differences between HIV-positive versus HIV-negative pregnant women included more sexual partners (5 vs. 2); higher rates of illicit drug use (50% vs. 0.78%), sex with foreigners (50% vs. 1.6%) STD rates (33% vs. 3.9%), sex with illicit drug users (25% vs. 3.1%), and receiving money for sex (50% vs. 0.52%).

**Conclusion**

Conclusion: Universal screening for HIV in pregnant Filipina women is not supported by the findings of this study despite the tremendous increase in HIV prevalence in the Philippines. A larger sample size may be useful to strengthen this assertion. Targeted HIV screening of pregnant women, particularly female sex workers, drug users and those with multiple partners should be offered.

*Acknowledgments: Supported with funding from the Department of Science and Technology – Philippine Council for Health Research and Development*

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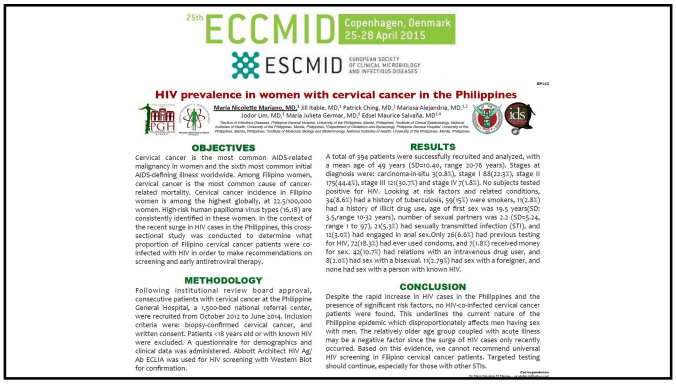


25th ECCMID Copenhagen, Denmark 25-28 April 2015
ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

**HIV prevalence in women with cervical cancer in the Philippines**

Maria Nicolette Mariano, MD,[1] Jill Ittable, MD,[1] Patrick Ching, MD,[1] Marissa Alejandria, MD,[1,2] Jodor Lim, MD,[1] Maria Julieta Germar, MD,[1] Edsel Maurice Salvaña, MD[1,2]

**OBJECTIVES**

Cervical cancer is the most common AIDS-related malignancy in women and the sixth most common initial AIDS-defining illness worldwide. Among Filipino women, cervical cancer is the most common cause of cancer-related mortality. Cervical cancer incidence in Filipino women is among the highest globally, at 22.5/100,000 women. High-risk human papilloma virus types (16,18) are consistently identified in these women. In the context of the recent surge in HIV cases in the Philippines, this cross-sectional study was conducted to determine what proportion of Filipino cervical cancer patients were co-infected with HIV in order to make recommendations on screening and early antiretroviral therapy.

**METHODOLOGY**

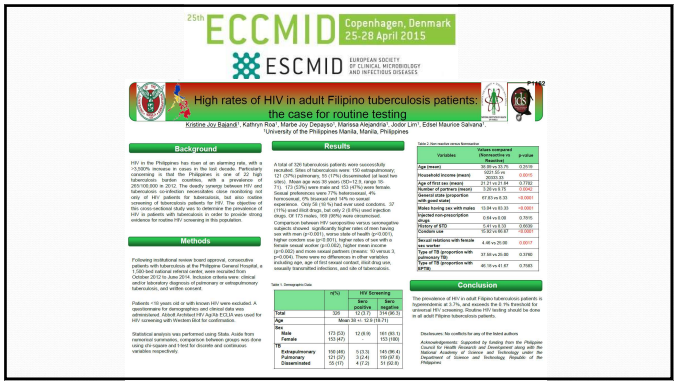
Following institutional review board approval, consecutive patients with cervical cancer at the Philippine General Hospital, a 1,500-bed national referral center, were recruited from October 2012 to June 2014. Inclusion criteria were: biopsy-confirmed cervical cancer, and written consent. Patients <18 years old or with known HIV were excluded. A questionnaire for demographics and clinical data was administered. Abbott Architect HIV Ag/Ab ECLIA was used for HIV screening with Western Blot for confirmation.

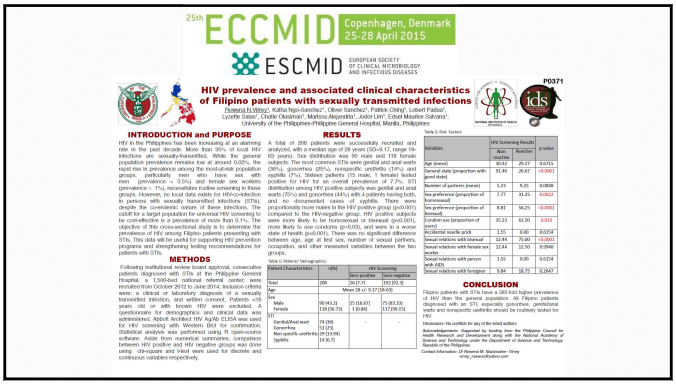
**RESULTS**

A total of 394 patients were successfully recruited and analyzed, with a mean age of 49 years (SD=10.40, range 20-76 years). Stages at diagnosis were: carcinoma-in-situ 30(8.1), stage I 88(23.3%), stage II 175(44.4%), stage III 121(30.7%) and stage IV 7(1.8%). No subjects tested positive for HIV. Looking at risk factors and related conditions, 34(8.61) had a history of tuberculosis, 59(15%) were smokers, 11(2.8%) had a history of illicit drug use, age of first sex was 19.5 years(SD: 3.5/range 10-32 years), number of sexual partners was 2.2 (SD=3.24, range 1 to 97), 21(5.3%) had sexually transmitted infection (STI), and 12(3.0%) had engaged in anal sex.Only 26(6.6%) had previous testing for HIV, 72(18.3%) had ever used condoms, and 7(1.8%) received money for sex. 42(10.7%) had relations with an intravenous drug user, and 8(2.0%) had sex with a bisexual. 11(2.79%) had sex with a foreigner, and none had sex with a person with known HIV.

**CONCLUSION**

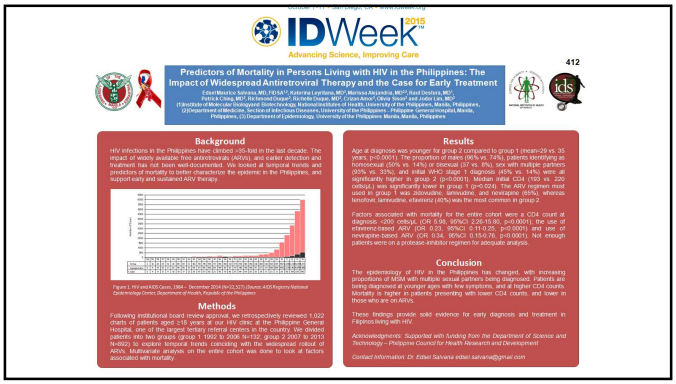
Despite the rapid increase in HIV cases in the Philippines and the presence of significant risk factors, no HIV-co-infected cervical cancer patients were found. This underlines the current nature of the Philippine epidemic which disproportionately affects men having sex with men. The relatively older age group coupled with acute illness may be a negative factor since the surge of HIV cases only recently occurred. Based on this evidence, we cannot recommend universal HIV screening in Filipino cervical cancer patients. Targeted testing should continue, especially for those with other STIs.




## Important points

- Prevalence of HIV in TB patients is 3.7% and in STI (sexually-transmitted infection) patients is 7.7%.
- No positives were detected in pregnant or cervical cancer patients.
- Solid evidence for universal screening in TB and STI patients




## Conclusion

- Factors associated with mortality for the entire cohort were a CD4 count at diagnosis <200 cells/μL (OR 5.98, 95%CI 2.26-15.80, p<0.0001);
- the use of efavirenz-based ARV (OR 0.23, 95%CI 0.11-0.25, p<0.0001) and
- use of nevirapine-based ARV (OR 0.34, 95%CI 0.15-0.76, p<0.0001).

## Transmission

- Blood-borne
- Sexual transmission
- Vertical transmission
- ? Breastmilk
- Theoretical risk with saliva to open wound, or human bite but no documented cases, one case of infection from deep kissing
- No risk from urine, feces, sweat or tears

## Risk from occupational exposure to patient with known disease

- HIV 0.3%
- HBV: HbSAg+ HbEAg+ 22-31%
  HbSAg+ HbEAg- 1-6%
- HCV 1.8%
- Prophylaxis for HIV available, but only works within 72 hours of exposure

- The risk of HIV transmission after injury with a hollow needle contaminated with HIV-infected blood is 0.3%
- The risk after injury with a suture needle is unknown.
- Increases in risk of transmission are associated with several specific circumstances : 16-fold if the hollow needle injury was a deep soft tissue penetration, 5-fold if there is either visible blood on the needle or the procedure involved placement of the needle in an artery or vein, and 6-fold if the patient has advanced AIDS

## Precautions for procedures

- Treat all patients as potentially infectious – universal precautions
- Protective eyewear, masks, and water-impermeable gowns, sleeves, and boots are standard equipment.
- Wearing two pairs of latex gloves reduces the risk of exposure due to glove defects from approximately 17% to 5%.
- During procedures involving open fractures, a pair of cloth gloves worn with latex gloves significantly reduces the risk of exposure.

- Avoidance of hand-to-hand passage of sharp instruments and increased use of staple devices instead of suturing are methods that reduce injury.
- Avoid using fingers for protecting underlying viscera to reduce injury from suture needle
- Blunted needles slowly gaining acceptance for fascial closure.
- For laparoscopy, be aware of the possibility of release of HIV-infected blood and peritoneal fluid into the operating room environment during pneumoperitoneal evacuation.

## Prevalence of exposure

- Prospective observational study of 1,307 consecutive patients at San Francisco General Hospital, accidental exposure of surgical personnel to patients' blood occurred during 84 procedures (6.4%)
- Parenteral exposure occurred during 23 procedures (1.7%). The risk of exposure was highest when procedures lasted more than 3 hours, when blood loss exceeded 300 mL, and when major vascular or intra-abdominal gynecologic surgery was performed

## Diagnosis

- HIV ELISA detects HIV antibody – screening test, highly sensitive (>99%), can sometimes have false positive
- Western Blot is confirmatory test
- Window period of 3 to 6 weeks from acute infection to development of antibodies
- HIV Ag/Ab test in PGH – around 20 days
- HIV PCR can detect virus around 5 days from infection

## HIV Testing

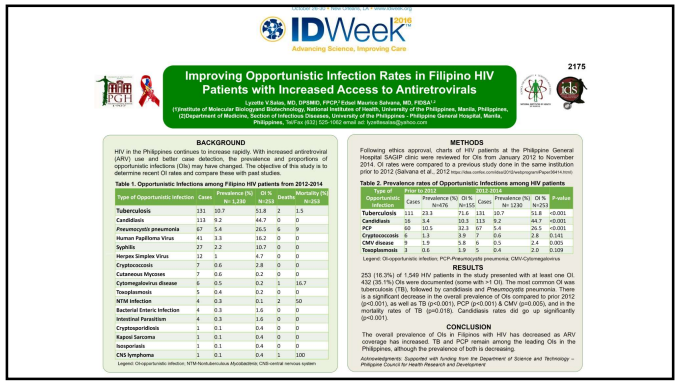
- Must be with full consent
- Confidential
- Can opt to use an alias
- If result is negative, can report to patient, if positive, WAIT FOR CONFIRMATORY TEST
- Never assume that patient's companions know his/her status

## Referral to treatment

- ARVs currently available only from treatment hubs, use in combination of 3 active drugs
- HIV treatment is complex and needs to be learned and studied if one wants to treat HIV patients
- Haphazard ARV use can lead to resistance or severe side effects
- Treatment of hepatitis B can lead to HIV resistance since HBV meds can affect HIV (clevudine, entecavir, lamivudine, tenofovir) – test all HBV patients for HIV before giving HBV treatment

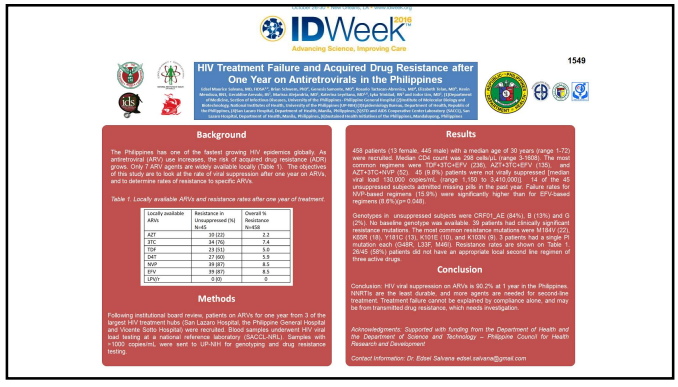
## Treatment

- Over 28 ARV agents available in US
- Only 5 (6) agents part of the national program:
  - NRTI – tenofovir, lamivudine, zidovudine
  - NNRTI – efavirenz, (nevirapine)
  - PI – lopinavir/ritonavir
- Available for fee: raltegravir
- For PrEP: tenofovir/emtricitabine



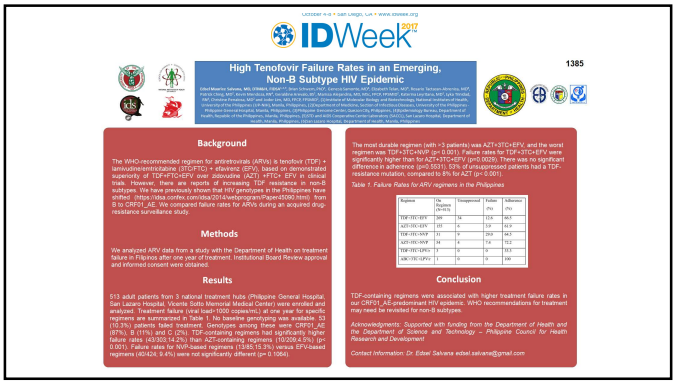

## Conclusions

- Since ARV rollout, OI rates significantly improved
- Lower rates of TB, PCP, and CMV
- Higher CD4 counts at diagnosis



## Important conclusions

- 84% CRF01_AE, 13% B
- Showed drug treatment failure rate at 1 year of antiretrovirals of 10.3%
- Showed concerning trend in tenofovir resistance
- Suggested possible transmitted drug resistance
- Showed that 57% of treatment failures without effective second-line




## Important conclusions

- High rate of treatment failure with tenofovir-based regimens
- Worst regimen: TDF+3TC+NVP (29%)
- Most durable: AZT+3TC+EFV (3.9%)
- 1st line: TDF+3TC+EFV (12.6%)
- May need to revisit WHO guidelines for non-B subtypes (distribution of failures: CRF01_AE 87%, B 11% and C 2%)

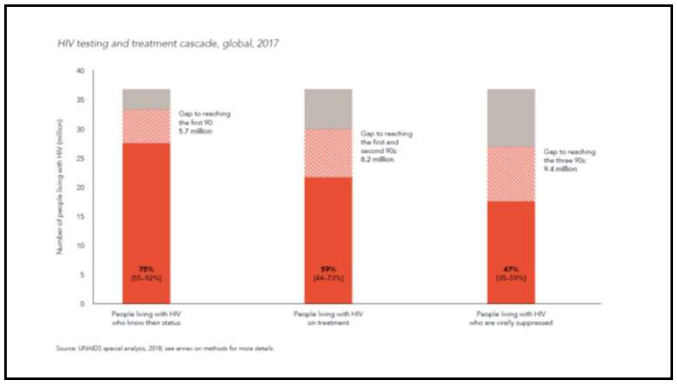
## Important conclusions

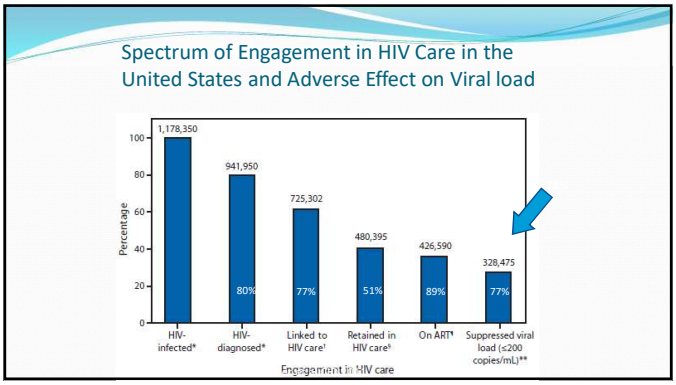
- Confirmed further shift to non-B subtype, particularly CRF01_AE
- TDR is present in 5.3% of treatment-naïve patients
- Above threshold for baseline genotype testing

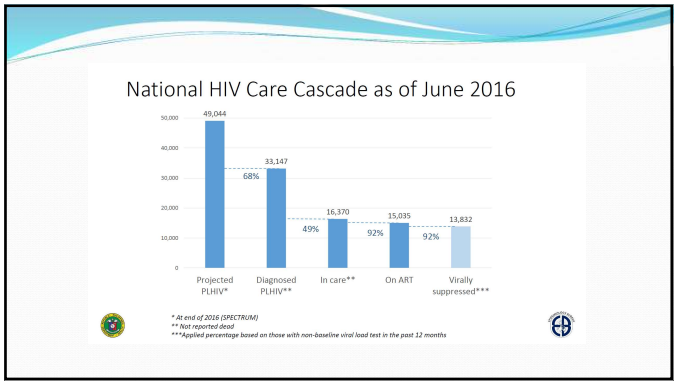
## HPTN 052 – Changing the Paradigm of HIV Treatment

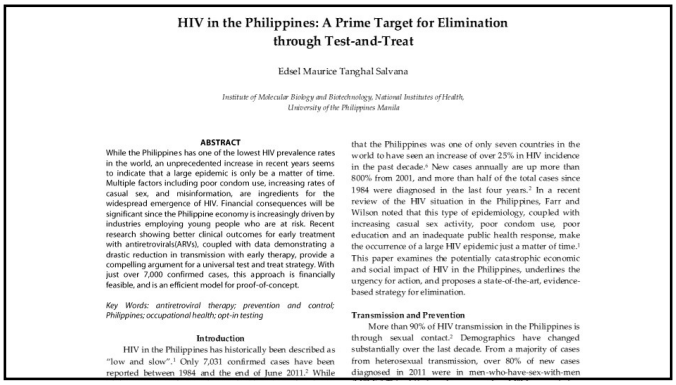

## HPTN 052 – Changing the Paradigm of HIV Treatment

- Recruited 1,763 HIV discordant couples (primarily heterosexual) from Malawi, Zimbabwe, Botswana, Kenya, South Africa, Thailand, US and India
- HIV-infected partner was randomized to immediate or deferred (when CD4 fell to 200-250 range) ART
- Median follow-up of 1.7 years; study halted prematurely by DSMB as immediate treatment reduced the risk of linked HIV transmission to the uninfected partner by 96%



**HIV in the Philippines: A Prime Target for Elimination through Test-and-Treat**

Edsel Maurice Tanghal Salvana

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**ABSTRACT**

While the Philippines has one of the lowest HIV prevalence rates in the world, an unprecedented increase in recent years seems to indicate that a large epidemic is only be a matter of time. Multiple factors including poor condom use, increasing rates of casual sex, and misinformation, are ingredients for the widespread emergence of HIV. Financial consequences will be significant since the Philippine economy is increasingly driven by industries employing young people who are at risk. Recent research showing better clinical outcomes for early treatment with antiretrovirals(ARVs), coupled with data demonstrating a drastic reduction in transmission with early therapy, provide a compelling argument for a universal test and treat strategy. With just over 7,000 confirmed cases, this approach is financially feasible, and is an efficient model for proof-of-concept.

*Key Words: antiretroviral therapy; prevention and control; Philippines; occupational health; opt-in testing*

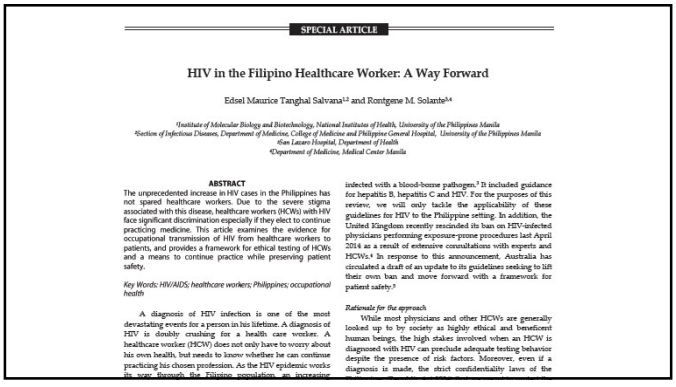
**Introduction**

HIV in the Philippines has historically been described as "low and slow".[1] Only 7,031 confirmed cases have been reported between 1984 and the end of June 2011.[2] While that the Philippines was one of only seven countries in the world to have seen an increase of over 25% in HIV incidence in the past decade.[3] New cases annually are up more than 800% from 2001, and more than half of the total cases since 1984 were diagnosed in the last four years.[2] In a recent review of the HIV situation in the Philippines, Farr and Wilson noted that this type of epidemiology, coupled with increasing casual sex activity, poor condom use, poor education and an inadequate public health response, make the occurrence of a large HIV epidemic just a matter of time.[1] This paper examines the potentially catastrophic economic and social impact of HIV in the Philippines, underlines the urgency for action, and proposes a state-of-the-art, evidence-based strategy for elimination.

**Transmission and Prevention**

More than 90% of HIV transmission in the Philippines is through sexual contact.[2] Demographics have changed substantially over the last decade. From a majority of cases from heterosexual transmission, over 80% of new cases diagnosed in 2011 were in men-who-have-sex-with-men

## Undetectable = Untransmissible

SPECIAL ARTICLE

**HIV in the Filipino Healthcare Worker: A Way Forward**

Edsel Maurice Tanghal Salvana[1,2] and Rontgene M. Solante[3,4]

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**ABSTRACT**

The unprecedented increase in HIV cases in the Philippines has not spared healthcare workers. Due to the severe stigma associated with this disease, healthcare workers (HCWs) with HIV face significant discrimination especially if they elect to continue practicing medicine. This article examines the evidence for occupational transmission of HIV from healthcare workers to patients, and provides a framework for ethical testing of HCWs and a means to continue practice while preserving patient safety.

*Key Words: HIV/AIDS; healthcare workers; Philippines; occupational health*

A diagnosis of HIV infection is one of the most devastating events for a person in his lifetime. A diagnosis of HIV is doubly crushing for a health care worker. A healthcare worker (HCW) does not only have to worry about his own health, but needs to know whether he can continue practicing his chosen profession. As the HIV epidemic works its way through the Filipino population, an increasing infected with a blood-borne pathogen.[3] It included guidance for hepatitis B, hepatitis C and HIV. For the purposes of this review, we will only tackle the applicability of these guidelines for HIV to the Philippine setting. In addition, the United Kingdom recently rescinded its ban on HIV-infected physicians performing exposure-prone procedures last April 2014 as a result of extensive consultations with experts and HCWs.[4] In response to this announcement, Australia has circulated a draft of an update to its guidelines seeking to lift their own ban and move forward with a framework for patient safety.[5]

*Rationale for the approach*

While most physicians and other HCWs are generally looked up to by society as highly ethical and beneficent human beings, the high stakes involved when an HCW is diagnosed with HIV can preclude adequate testing behavior despite the presence of risk factors. Moreover, even if a diagnosis is made, the strict confidentiality laws of the

**Table 1. Category I: a list of categories of procedures with de minimis risk of viral transmission.**

| |
|---|
| Regular history-taking and/or physical examinations, including gloved oral examination with a mirror and/or tongue depressor |
| Routine rectal or vaginal examinations |
| Minor surface suturing |
| Elective peripheral phlebotomy[a] |
| Lower gastrointestinal tract endoscopic examinations and procedures, such as sigmoidoscopy and colonoscopy |
| Hands-off supervision during surgical procedures and computer-aided remote or robotic surgical procedures |
| Psychiatric evaluations[b] |

[a] If done in an emergency situation (e.g., during acute trauma or resuscitation efforts), peripheral phlebotomy moves to category III.
[b] If there is no risk present of biting or of otherwise violent patients.

**Table 2. Category II: a list of categories of procedures for which viral transmission is theoretically possible but unlikely.**

| |
|---|
| Procedures that warrant general attention |
| Locally anesthetized ophthalmologic surgery |
| Minor local procedures (e.g., skin excisions, abscess drainage, biopsies, and use of laser) under local anesthesia (often under bloodless conditions) |
| Percutaneous cardiological procedures (e.g., angiography and catheterization) |
| Percutaneous and other minor orthopedic procedures |
| Subcutaneous pacemaker implantation |
| Bronchoscopy |
| Insertion and maintenance of epidural and spinal anesthesia lines |
| Minor gynecological procedures (e.g., dilatation and curettage, suction abortion, colposcopy, inserting and removing contraceptive devices and implants, and collecting ova) |
| Male urological procedures (excluding transabdominal intrapelvic procedures) |
| Upper gastrointestinal tract endoscopic procedures |
| Minor vascular procedures (e.g., embolectomy and vein stripping) |
| Amputations, including major limbs (e.g., hemipelvectomy and amputation of legs or arms) and minor amputations (e.g., amputations of fingers, toes, hands, or feet) |
| Mamma augmentation |
| Minimum-exposure plastic surgical procedures (e.g., liposuction, minor skin resections for reshaping, face lift, brow lift, blepharoplasty, and otoplasty) |
| Thyroidectomy and/or biopsy |
| Endoscopic ear, nose, and throat surgery and simple ear and nasal procedures (e.g., stapedectomy/stapedotomy and insertion of tympanic tubes) |
| Procedures that warrant special attention |
| Assistance with at uncomplicated vaginal delivery[a] |
| Laparoscopic procedures |
| Thoracoscopic procedures[b] |
| Nasal endoscopic procedures[c] |
| Routine arthroscopic procedures[d] |
| Plastic surgery[e] |
| Insertion of, maintenance of, and drug administration into arterial and central venous lines |
| Endotracheal intubation and use of laryngeal mask |

**Table 3. Category III: a list of categories of procedures for which there is definite risk of viral transmission or that are exposure-prone procedures.**

| Procedure or field | Specific procedures and incidents |
|---|---|
| Abdominal surgery | For HBV, elective nephrectomy; small bowel resection, elective cholecystectomy, subtotal thyroidectomy (2 patients [14] and 3 patients [59]; unspecified surgery (3 patients [60]); other elective open abdominal surgery |
| Anesthesiology | For HCV, administration of general anesthesia, preparation of narcotic drugs, placement of venous and arterial catheters, intubation of patients, and artificial respiration (5 patients [18] and 217 patients [16]) |
| Cardiothoracic surgery | For HBV, unspecified procedure (5 patients [4]); valve replacement, coronary artery bypass grafting, other bypass surgery, orthoptic heart transplantation, repair of congenital heart defects, thymectomy, open-lung biopsy (17 proven infected patients of 361 researched cases of potential viral transmission [2] and 19 of 144 [59]); for HCV, unspecified (1 patient [20]; 1 patient, for a 0.36% transmission rate [17]; 3–7 of 3000 [21]) and valve replacement (5 of 222 [15]) |
| Open extensive head and neck surgery involving bones | Oncological procedures and amputations |
| Neurosurgery | Craniotomy and intracranial procedures and open-spine surgery |
| Nonelective procedures performed in the emergency department | Open resuscitation efforts, vaginal or rectal examination in presence of pelvic fracture, deep suturing, to arrest hemorrhage, and internal cardiac massage |
| Obstetrical/gynecological surgery | For HBV, Cesarean section, hysterectomy, forceps delivery, episiotomy, cone biopsy, and ovarian cyst removal (22 of 247, for a 9% overall transmission rate [1], 2 patients [14]); other unspecified gynecological surgery (8 of 589 and 9 of 1026 [6]); for HCV, unspecified (1 patient [19]) and other transvaginal obstetrical and gynecological procedures involving handguided sharps (e.g., cone biopsies involving suturing, administering local anesthetic to cervix, and attaching scalp electrodes to baby's head during delivery) |
| Orthopedic procedures | For HBV, total knee arthroplasty (8); for HIV, total hip arthroplasty (1 of 983 [22]), major joint replacement surgery (e.g., hip, knee, shoulder, and elbow), open spine surgery, and open pelvic surgery |
| Plastic surgery | Extensive cosmetic procedures (e.g., abdominoplasty, breast reduction, and thigh plasty) |
| Psychiatric evaluations and care of violent and/or biting patients | ... |
| Transplantation surgery | ... |
| Trauma surgery | Including open head injuries, extensive soft-tissue trauma, and ophthalmic trauma |
| Interactions with patients in situations during which risk of biting of physician is significant | For example, interactions with violent patients or patients experiencing an epileptic seizure |
| Any open surgical procedure of >3 h in duration, probably necessitating glove change | ... |

**Table 4. Decision chart for safe-practice management for infected physicians who perform invasive procedures.**

| | | Agent of infection | | | |
|---|---|---|---|---|---|
| | | HBV | | HCV | |
| Category | HIV | A[a] | B[b] | A[c] | B[c] |
| I | No restrictions | No restrictions | No restrictions | No restrictions | No restrictions |
| II | No restrictions | No restrictions | Do not attempt[e] | No restrictions | Do not attempt[e] |
| III | Do not attempt | Do not attempt | Do not attempt | Do not attempt | Do not attempt |

**NOTE.** HBV, hepatitis B virus; HCV, hepatitis C virus.
[a] Presence of the 3 following characteristics: HBV e antigen negative, viral load of $<10^3$ genome equivalents/mL, and DNA negative.
[b] Presence of 1 of the 3 following characteristics: HBV e antigen positive, viral load of $\geq 10^5$ genome equivalents/mL, or DNA positive.
[c] Viral load was detectable but $<10^4$ virions/mL.
[d] High viral load ($\geq 10^4$ virions/mL).
[e] This is highly specialty- and procedure-specific. A number of procedures in category II will be relatively safe to perform even by more-infectious physicians. However, those procedures that may move into category III while being performed or that are within a range of procedures that are inherently connected are not relatively safe. It would be exceedingly cumbersome—not to say practically impossible—for an infected physician to effectively perform the full range of necessary procedures while refraining from unsafe actions. Examples of such situations include obstetrical/gynecological surgery including unexpectedly complicated deliveries, laparoscopy, thoracoscopy, and arthroscopy, which are footnoted in the category II list. Therefore, most category II procedures are not to be attempted by physicians in group B. However, if a qualified and noninfected physician or physician from group A is available to take over in case such procedures move to category III, they may be performed by physicians in group B. Admittedly, this is a complicated scenario, but it aims to err on the safe side while not unduly restricting group B physicians.

HIV Cure

**THE CURE "IMPOSSIBLE" ERA: 1997-2009**

*Science* Vol 278*14 November 1997

**Identification of a Reservoir for HIV-1 in Patients on Highly Active Antiretroviral Therapy**

Diana Finzi, Monika Hermankova, Theodore Pierson, Lucy M. Carruth, Christopher Buck, Richard E. Chaisson, Thomas C. Quinn, Karen Chadwick, Joseph Margolick, Ronald Brookmeyer, Joel Gallant, Martin Markowitz, David D. Ho, Douglas D. Richman, Robert F. Siliciano*

**Recovery of Replication-Competent HIV Despite Prolonged Suppression of Plasma Viremia**

Joseph K. Wong,* Marjan Hezareh, Huldrych F. Günthard, Diane V. Havlir, Caroline C. Ignacio, Celsa A. Spina, Douglas D. Richman

*Proc. Natl. Acad. Sci. USA*
Vol. 94, pp. 13105–13107, November 1997
Medical Sciences

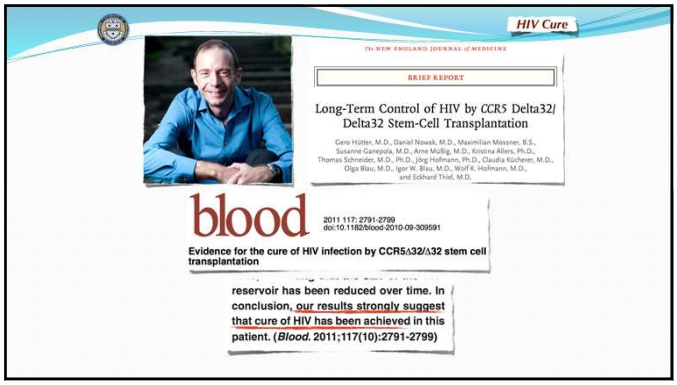
**Presence of an inducible HIV-1 latent reservoir during highly active antiretroviral therapy**

TAE-WOOK CHUN*†, LIEVEN STUYVER‡, STEPHANIE B. MIZELL*, LINDA A. EHLER*, JO ANN M. MICAN*, MICHAEL BASELER§, ALUN L. LLOYD§, MARTIN A. NOWAK§, AND ANTHONY S. FAUCI*

Latent HIV reservoir that decays with a $T_{1/2}$ of 44 months

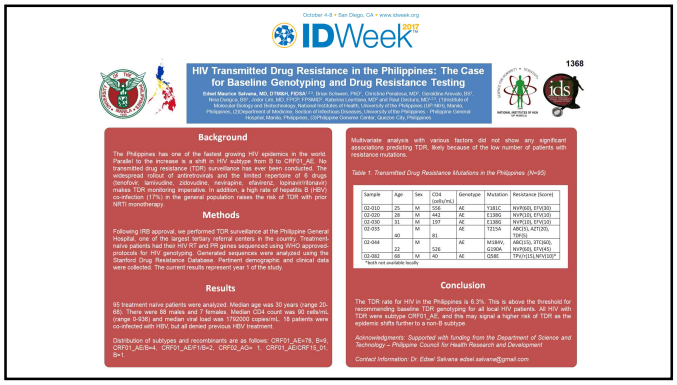
## HIV Cure

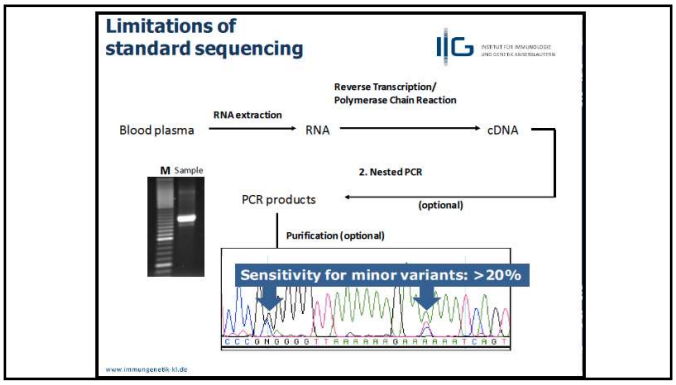
- Timothy Ray Brown - 'The Berlin Patient"
  - HIV infected in 1995; began ART 2006
  - Diagnosed with AML in 2008 and underwent SCT x 2 with HLA matching and delta 32 CCR5 mutation
  - Had GVHD disease as well
  - Remains off ART x 7 years with no HIV detectable in blood or multiple tissues; considered a "sterilizing cure

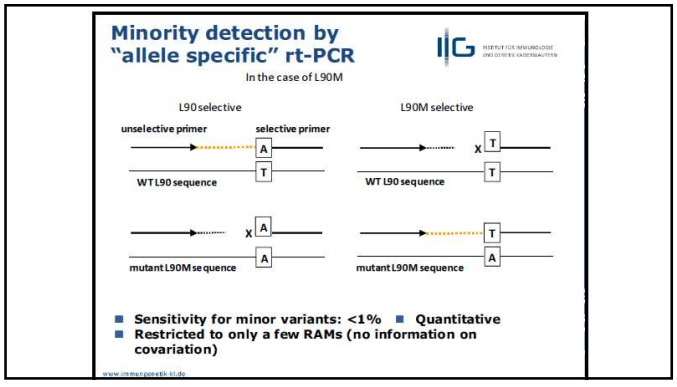



## Ongoing Research

- NGS of 300 newly diagnosed HIV patients to look for transmitted drug resistance and recombinants
- Abstract with preliminary results presented at ID Week 2017 San Diego



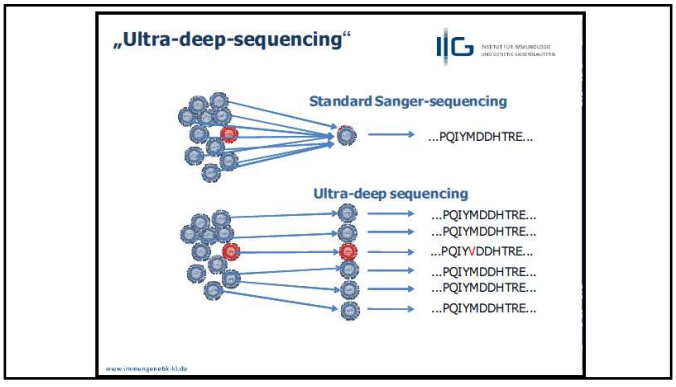
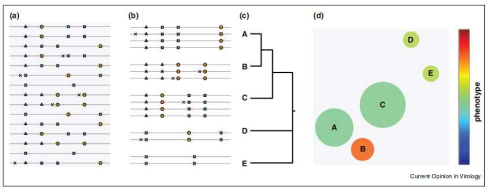



Figure 1




Analysis of viral quasispecies. A schematic representation of an intra-host virus population is displayed in **(a)**, where each line corresponds to a haplotype and symbols indicate differences relative to a reference strain. In local haplotype reconstruction, all reads cover the sequence window. Once reads are clustered, it is easier to distinguish technical errors (crosses) from true biological variations (all other symbols). Haplotypes are identified as the consensus sequences of each group (denoted A, …, E) and their frequencies as the cluster sizes **(b)**. The reconstructed viral quasispecies can then be further analyzed, for example, by phylogenetic methods **(c)**. In **(d)**, the virus population is displayed such that the size of each disc corresponds to the proportion of the respective haplotype in the population and the distances between them reflect evolutionary distance. The color coding suggests that haplotypes may be annotated with phenotypic properties, for example the level of drug resistance [32••].

## Summary

- HIV epidemic is increasing, patients are getting younger, and demographics are shifting
- Effective treatment is available and can interrupt transmission
- HIV molecular subtype has shifted, and response to treatment may be different from Western subtypes
- Subtype shift seen in the Philippines may occur in other countries with concomitant explosion in cases
- Need to harness new findings and increased awareness campaign to get people tested and access care to reverse the epidemic

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## Thank you