A prospective longitudinal cohort study to determine the incidence of HIV-associated non-AIDS conditions in newly diagnosed HIV-infected individuals initiating integrase inhibitor-based and other anti-retroviral regimens

Background

Integrase strand transfer inhibitor (INSTI) based–therapy is currently the recommended antiretroviral regimen in most guidelines.[1-3] Efficacy in terms of virological suppression of INSTI-based regimens was either superior or non-inferior to other comparators in clinical trials performed in both treatment naïve and experienced individuals.[4-6] Moreover, unlike other classes of anti-retroviral agents, transmitted drug resistance was uncommon even after years of introduction of INSTI on a population level, potentially allowing this class of drug to remain as recommended first-line treatment in the future.[7]

Previous clinical trials comparing INSTIs and other anti-retroviral regimens in treatment-naïve individuals consistently showed lower discontinuation rates secondary to adverse reactions.[4,8,9] For treatment-experienced individuals, switching from non-nucleotide reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI)-containing to an INSTI-containing regimen often resulted in better lipid profiles[6] as well as tolerability and patient satisfaction.[5] INSTIs have been shown to improve blood pressure control in those with underlying hypertension receiving anti-hypertensive treatment.[10] INSTI also had lesser decline in bone loss when compared to protease inhibitors.[11] On the other hand, integrase inhibitors have been reported to be the cause of metabolic complications,[12] and neuropsychiatric adverse reactions.[13] Transient drop in renal function[6] and other renal complications in individuals taking some INSTIs had also been reported.[14]

Currently, with the availability of very effective anti-retroviral agents as well as aging of the HIV-infected population, management of HIV-infected individuals should also include the assessment, prevention and management of multiple HIV-associated non-AIDS conditions (HANA) that are known to be more prevalent in HIV-infected individuals.[15] In Asia, many of these conditions, like diabetes,[16] dyslipidemia,[17] lipodystrophy,[17] osteopenia and osteoporosis,[18] chronic kidney disease,[19] and fatty liver disease and liver fibrosis,[20] and retinal diseases[21,22] were prevalent in HIV-infected individuals. Most of these studies, however, were performed in individuals taking older anti-retroviral agents. Whether the increase of INSTI use in the region is associated with lower incidence of development of HANA is currently unknown. Moreover, clinical trials of anti-retroviral therapy seldom included older individuals with multiple co-morbid illnesses.[4] Currently available real world data on clinical use of INSTI seldom included HANA in their evaluation.[14, 23, 24] Longitudinal real world data in Asia evaluating the incidence of various HANA after initiation of different anti-retroviral regimens are also limited, despite these conditions cause significant burden of disease in the Asian population.[15]

The understanding of incidence of various HANA conditions in relation to the class of anti-retroviral drugs used will potentially aid to improve outcomes in the aging HIV-infected population by optimizing their anti-retroviral regimen. As data on HANA in the Asian/Chinese HIV-infected population is currently lacking, results of studies performed in Hong Kong which mainly comprises of predominantly Chinese and other Southeast/South Asian HIV-infected

individuals, would likely benefit other HIV-infected populations in China, Taiwan and other surrounding Asian countries.

This study, therefore, aims to evaluate the incidence of various HANA conditions in a cohort of newly diagnosed HIV-infected individuals in Hong Kong initiating anti-retroviral treatment. The incidence of various HANA conditions will be evaluated for those receiving INSTI versus other non-INSTI-based regimens.

Objectives

- To determine the incidence of HANA conditions in newly diagnosed HIV-infected individuals initiating integrase inhibitor-based and other anti-retroviral regimens in an Asian population
- To evaluate the risk factors associated with developing each HANA condition
- To set up an electronic platform for systematic collection of clinical data and establishment of a clinical decision tool for clinical risk prediction and improvement in clinical management

Clinical hypotheses

Individuals initiating integrase inhibitor-based anti-retroviral regimens will develop lower incidence of HANA.

Study design

This is a prospective, longitudinal, cohort study. 400 newly diagnosed HIV-infected individuals attending HIV clinics in Hong Kong will be recruited. Clinical assessment, and laboratory and imaging studies will be performed at baseline prior to initiation of anti-retroviral regimen, than annually thereafter for 5 years. Choice of anti-retroviral regimen will be decided by the in-charge HIV physician. Incidence of development of various HANA conditions will be determined for those initiated INSTI-based regimens and other anti-retroviral regimens. An electronic platform will be used to formulate risk prediction for various clinical outcomes, and serve as a clinical decision support tool.

Subjects and sampling

a. Study population
   All newly diagnosed HIV-infected individuals naïve to ART meeting inclusion criteria, who attend the government HIV clinic, which is the largest HIV clinic in Hong Kong, will be invited to participate in this study. Subjects will also be referred by non-governmental organizations providing support to HIV-infected individuals at the time of diagnosis.
b. Inclusion criteria:
   1. Confirmed HIV infection by HIV antibody or RNA test
   2. Age ≥18 years old
   3. Anti-retroviral treatment naïve, within 6 months of initiation of anti-retroviral drugs, or switching ART regimens within 24 months
   4. Agree to initiate anti-retroviral therapy (ART) as determined by in-charge HIV physician
c. Exclusion criteria:
   1. Pregnancy
   2. Refusal to consent

Data collection and investigations

a. Eligible subjects will attend Infectious Diseases clinic at the Prince of Wales Hospital for assessment.

The first study visit will be scheduled before or within four weeks of initiation of ART. Annual visits will be scheduled thereafter for 5 years. During each study visit, demographic and clinical data will be collected. Physical examination will be performed. Blood and urine tests will be done at fasting state. Imaging, including ultrasonography of carotid arteries, DEXA scan and fibroscan, will be performed. Stool samples will be collected for microbiota study.

b. Clinical data

   A structured standardized research tool will be used to collect demographic and clinical data:

   1. Age, gender, smoking status, alcohol consumption, exercise
   2. Co-morbid illnesses, including history or new diagnoses of hepatitis B and C, diabetes, dyslipidemia, hypertension, metabolic syndrome, and cardiovascular diseases, as well as all comorbidities included in the Charlson comorbidity score
   3. Date of HIV diagnosis, latest CD4 counts, latest HIV viral load
   4. Medication history, including anti-retroviral drugs and other medications

c. Physical examination and anthropometric measurements

   1. Body weight and height, and body mass index
   2. Hip and waist circumferences
   3. Blood pressure
   4. For subjects aged ≥50 years old, assessment of frailty, including hand grip strength, balance tests, 6-metre walking speed, will be performed
   5. Neurocognitive assessment
      i. International HIV dementia scale https://www.hiv.uw.edu/page/mental-health-screening/ihds[25]
      ii. Montreal Cognitive Assessment
      iii. Symbol digit modality test (SDMT)
      iv. Action fluency: ask the patient to say as many things that people do in 1 minute
      v. Cogstate platform neurocognitive tests
      vi. DASS 21 for screening of mood
      vii. Lawton Instrumental Activities of Daily Living
   6. Quality of life assessment
      i. EQ-5D-5L questionnaire
   7. Lung function test
      i. FEV1 and FVC will be performed in smokers.

d. Blood tests:

   The following blood tests will be performed after an 8-hour fast:

   1. Glucose, insulin, HbA1c
   2. Total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, apolipoprotein A and apolipoprotein E
   3. Complete blood count, creatinine, urate, calcium, phosphate, urea, ferritin
   4. Testosterone, estradiol, luteinizing hormone, follicle-stimulating hormone, free thyroxine, thyrotropin, growth hormone, cortisol
   5. 25(OH) vitamin D, parathyroid hormone, calcium, alkaline phosphatase
   6. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelet count,

bilirubin, albumin
7. Adiponectin, leptin
8. Quantitative immunoglobulins, serum paraproteins
9. sCD14, hsCRP, IL-6, D-dimer, sVCAM-1, sICAM, TNF-a
10. HBsAg, anti-HBc, anti-HCV antibody
11. Cytokeratin-18 fragments using M30-Apoptosense ELISA kit (PEVIVA, Bromma, Sweden) as a marker for steatohepatitis

e. Spot urine tests for:
1. Phosphate, urate, creatinine
2. Retinol-binding protein (RBP), β2 microglobulin
3. Protein and albumin

f. Ultrasonography of carotid arteries
1. Carotid IMT (cIMT) will be measured to provide estimates on atherosclerosis extent and progression.[26] B-mode ultrasound examinations will be performed with Vivid E9 (GE Healthcare, Milwaukee, WI, USA) with a 11 MHz scanning frequency linear transducer. All scans will be performed by an experienced physician after a predetermined, standardized scanning protocol for the posterior wall of right and left carotid arteries using images of the far wall of the distal 10mm of the common carotid arteries. The reported cIMT value represents the mean of measurements at both left and right carotid arteries. A carotid plaque will be considered to be present when cIMT was >1.2 mm at any site.

g. Dual energy absorptiometry (DEXA) scan:
1. Site-specific bone DEXA will be performed using a Hologic QDR 4500A fan beam densitometer (Hologic, Inc., Bedford, MA) to measure hip and lumbar spine (from L1 to L4) bone mineral density (BMD) and lumbar spine trabecular bone score.
2. Whole body DEXA will be performed to measure total body fat, lean body mass, and regional fat in arms, legs, and trunk (in grams). In measuring trunk fat, a line of delineation will be drawn between the head of the humerus and the glenoid fossa of the scapula to separate the upper limb from the trunk, and the leg consists of the parts of the body between the inferior border of the ischial tuberosity to the most distal tip of the toes.

h. Fibroscan
1. Liver stiffness measurement by transient elastography will be performed. Ten successful acquisitions will be performed on each subject. The median value represents the liver elastic modulus. Liver stiffness will be expressed in kiloPascal (kPa). Liver stiffness measurements will be considered valid only if 10 successful acquisitions are obtained, and the interquartile range (IQR) to median ratio of the 10 acquisitions is <0.3. Only valid liver stiffness measurements were included in the analyses involving liver stiffness.[20]
2. Controlled attenuation parameter (CAP) will be used to measure liver ultrasonic attenuation, for determination of hepatic steatosis. CAP will be computed only when the associated liver stiffness measurement is valid and using the same signals as the one used to measure liver stiffness. The final CAP value is the median of individual CAP values and will be expressed in dB/m.[27]

i. Automated retinal image analysis
1. Digital fundus photographs will be acquired by a trained technician using a Canon CR2 AF non-mydriatic retinal camera of both eyes (Canon). Retinal vessel

measurements will be made. ARIA-stroke risk score will be calculated.

j. Risk prediction
    1. Cardiovascular
        i. 10-year risk of developing atherosclerotic cardiovascular disease will be calculated based on the Pooled Cohort ASCVD Risk Equations.[28]
        ii. Cardiovascular disease risk will be calculated using the DAD cohort risk prediction equation http://www.hivpv.org/Home/Tools/tabid/91/ctl/ExamView/mid/500/eid/0/lid/0/Default.aspx
    2. Renal disease
        i. Risk of developing chronic kidney disease will be calculated based on the following risk scores:
        ii. DAD risk prediction https://www.chip.dk/Tools-Standards/Clinical-risk-scores[29]
        iii. UCSF risk prediction http://hivinsite.ucsf.edu/InSite?page=md-calculator[30]
    3. Osteoporosis/fracture
        i. 10-year risk of fracture will be calculated using WHO Fracture Risk Assessment Tool (FRAX) score: http://www.shef.ac.uk/FRAX/
    4. Cognitive impairment
        i. HIV international dementia scale ≤10
    5. Mood
        i. Depression score >9, anxiety score >7, or stress score >14 according to DASS 21 assessment

Outcome measures

HANA conditions will be defined as follows:

a. Cardiovascular diseases
    1. Diagnosis of coronary heart disease, cerebrovascular disease, or peripheral artery disease by physician supported by relevant imaging results
    2. Subclinical atherosclerosis
        i. Presence of plaques on carotid arteries
        ii. cIMT greater than 75th percentile of population
b. Diabetes and pre-DM
    1. DM will be defined by fasting glucose ≥ 7.0 mmol/L, or HbA1c ≥6.5%.[31]
    2. Pre-DM will be defined by fasting glucose 5.6-6.9 mmol/L, or HbA1c 5.7-6.4% [32]
    3. Insulin resistance will be defined by HOMA-insulin resistance (fasting insulin (μU/ml)/22.5*(glucose (mmol/l)) >2.5 [33]
c. Hypertension
    1. Systolic blood pressure ≥130mmHg, or diastolic blood pressure ≥80mmHg[34]
d. Metabolic syndrome
    1. Metabolic syndrome will be defined according to ethnic-specific criteria by the International Diabetes Federation, as any three of the following: (1) central obesity (waist circumference ≥90cm in men and ≥80cm in women); (2) triglycerides >1.7mmol/l; (3) reduced HDL cholesterol (<1.03mmol/l in men and <1.29mmol/l in women); (4) blood pressure ≥130/85mm Hg; and (5) fasting plasma glucose ≥5.6mmol/l; or receiving treatment for the above metabolic abnormalities.[35]
e. Obesity
    1. Overweight will be defined as BMI >23 kg/m^2 [36]

2. Obesity will be defined as BMI >26 kg/m^2 [36]

f. Fatty liver and liver fibrosis
   1. Fatty liver will be expressed as CAP in dB/m, and hepatic steatosis grading will be defined as mild if CAP is 248-267 dB/m, moderate if 268-279 dB/m, and severe if ≥280 dB/m[37]
   2. Liver stiffness will be expressed in kiloPascal (kPa). LS>9.6-11.5kPa will be considered as advanced fibrosis, and LS>11.5kPa as cirrhosis[38]

g. Renal disease
   1. Glomerular filtration rate (GFR) will be calculated using the 2009 CKD-EPI creatinine equation. Renal impairment will be defined as GFR <90 ml/min, and albuminuria will be defined as urine albumin/Creatinine ratio ≥30mg/g, according to KDIGO 2012 clinical practice guideline.[39]
   2. Kidney tubular dysfunction will be defined by:[40]
      i. Fractional tubular resorption of phosphate {1- [(urine phosphate x serum Cr)/(urine Cr x serum phosphate)]}x100 of <82%;
      ii. Fractional excretion of uric acid {[(urine uric acid x serum Cr)/(urine Cr x serum uric acid)] x 100} of >15%;
      iii. β2-microglobulin:creatinine > 1000 μg/g Cr; or
      iv. RBP:creatinine >17μg/mmol Cr

h. Osteopenia and osteoporosis
   1. Osteoporosis is defined, according to World Health Organization criteria, as BMD T-score of ≤2.5 at the hip or spine in men ≥50 years old and post-menopausal women, or Z-score of ≤2.0 in men younger than 50 years old and pre-menopausal women.[41]
   2. Osteopenia is defined as a T-score between 1 and 2.49.[41]

i. Chronic obstructive airway disease
   1. FEV1/FVC <0.7

j. Frailty and sarcopenia in those aged 50 and above
   1. Frailty is defined by Frailty phenotype measurement, according to Fried definition[42]

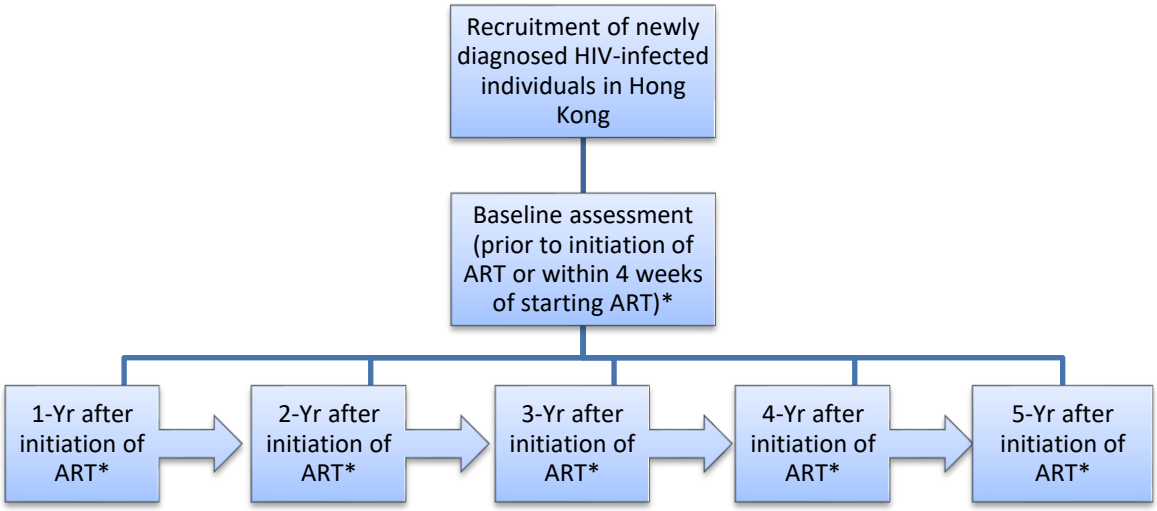
k. Sarcopenia is defined as appendicular lean mass (kg)/height^2(m^2) < 2 standard deviations below the mean for young healthy adults (cut-offs were < 7.26 kg/m^2 for men and < 5.45 kg/m2 for women)[43]

l. Retinal vasculopathy
   1. Presence of HIV retinopathy, retinal vein occlusions and retinal artery occlusions

Electronic platform

a. An electronic database will be established for systematic collection of all the above clinical and laboratory data, and clinical outcomes.
b. The collected data will be used to generate risk assessment for multiple HANA conditions. Clinical management will be recommended according to risk assessment.
c. A report summarizing the risk assessment and diagnosis of each HANA condition will be generated for each patient after each study visit. The report will be submitted to their HIV physicians for further clinical management.

Study Flowchart



*During each study visit, demographic and clinical data will be collected. Physical examination will be performed. Blood and urine tests will be done at fasting state. Imaging, including ultrasonography of carotid arteries, DEXA scan and fibroscan, will be performed. Stool samples will be collected for microbiota study.

Sample size calculation

There were around 700 new HIV infections reported in Hong Kong in 2015 and 2016. Based on previous published data,[44] the risk of developing metabolic syndrome is approximately 20% at 96 weeks after initiation of ART, a sample size of 400 will give a 95% confidence interval from 16% to 24% at 96 weeks. Using the same 400 patients, we would be able to detect with 95% confidence an odds ratio of 2 for any risk factors with respect to the incidence of metabolic syndrome assuming that the prevalence is 20% and we would like to have an estimate of the population odds ratio to within 50% of the true value (i.e. a lower bound of 1.0 for the 95% confidence interval of the odds ratio) even after adjusted for type I error due to multiple risk factors.[45]

Statistical analysis

a. The incidence rate of each HANA defined as above will be calculated as:

$$incidence\ rate\ of\ HANA\ (per\ 100\ person-years) = \frac{number\ of\ new\ diagnosis\ of\ HANA\ at\ end\ of\ follow\ up}{\text{number of persons at risk} * \text{number of years of follow up}}\ x\ 100$$

b. The incidence rate of each HANA will be determined for subjects started INSTI-based regimens and other non-INSTI-anti-retroviral regimens.

c. Variables, including demographic, clinical, treatment-related, and laboratory parameters, will be evaluated for association with development of various HANA, in univariate and multivariate analyses. Analyses will be performed for the whole cohort, and subgroup analyses will be performed in those initiated INSTI-based regimens and other non-INSTI-based regimens.

Study Conduct

This study will be conducted in accordance with Declaration of Helsinki.

References

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and HumanServices. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed 15 Mar 2017.
2. Günthard HF, Saag MS, Benson CA, del Rio C, Eron JJ, Gallant JE, Hoy JF, Mugavero MJ, Sax PE, Thompson MA, Gandhi RT, Landovitz RJ, Smith DM, Jacobsen DM, Volberding PA. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2016 Recommendations of the International Antiviral Society-USA Panel. JAMA. 2016 Jul 12;316(2):191-210
3. EACS guidelines verson 8.1. http://www.eacsociety.org/files/guidelines_8.1-english.pdf. Accessed 15 Mar 2017.
4. Rutherford GW, Horvath H. Dolutegravir Plus Two Nucleoside Reverse Transcriptase Inhibitors versus Efavirenz Plus Two Nucleoside Reverse Transcriptase Inhibitors As Initial Antiretroviral Therapy for People with HIV: A Systematic Review. PLoS One. 2016 Oct 13;11(10):e0162775.
5. Raffi F, Esser S, Nunnari G, Pérez-Valero I, Waters L. Switching regimens in virologically suppressed HIV-1-infected patients: evidence base and rationale for integrase strand transfer inhibitor (INSTI)-containing regimens. HIV Med. 2016 Oct;17 Suppl 5:3-16. doi: 10.1111/hiv.12440.
6. Wong E, Trustman N, Yalong A. HIV pharmacotherapy: A review of integrase inhibitors. JAAPA. 2016 Feb;29(2):36-40. doi: 10.1097/01.
7. Scherrer AU, Yang WL, Kouyos RD, Böni J, Yerly S, Klimkait T, Aubert V, Cavassini M, Battegay M, Hauser C, Calmy A, Schmid P, Bernasconi E, Günthard HF; Swiss HIV Cohort Study. Successful Prevention of Transmission of Integrase Resistance in the Swiss HIV Cohort Study. J Infect Dis. 2016 Aug 1;214(3):399-402.
8. Kanters S, Vitoria M, Doherty M, Socias ME, Ford N, Forrest JI, Popoff E, Bansback N, Nsanzimana S, Thorlund K, Mills EJ. Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta-analysis. Lancet HIV. 2016 Nov;3(11):e510-e520.
9. Squires K, Kityo C, Hodder S, Johnson M, Voronin E, Hagins D, Avihingsanon A, Koenig E, Jiang S, White K, Cheng A, Szwarcberg J, Cao H. Integrase inhibitor versus protease inhibitor based regimen for HIV-1 infected women (WAVES): a randomised, controlled, double-blind, phase 3 study. Lancet HIV. 2016 Sep;3(9):e410-20.
10. De Socio GV, Ricci E, Maggi P, Parruti G, Celesia BM, Orofino G, Madeddu G, Martinelli C, Menzaghi B, Taramasso L, Bonfanti P, Pucci G, Schillaci G; CISAI study group. Time trend in hypertension prevalence, awareness, treatment, and control in a contemporary cohort of HIV-infected patients: the HIV and Hypertension Study. J Hypertens. 2017 Feb;35(2):409-416
11. Brown TT, Moser C, Currier JS, Ribaudo HJ, Rothenberg J, Kelesidis T, Yang O, Dubé MP, Murphy RL, Stein JH, McComsey GA. Changes in Bone Mineral Density After Initiation of Antiretroviral Treatment With Tenofovir Disoproxil Fumarate/Emtricitabine Plus Atazanavir/Ritonavir, Darunavir/Ritonavir, or Raltegravir. J Infect Dis. 2015 Oct 15;212(8):1241-9.
12. Fong PS, Flynn DM, Evans CD, Korthuis PT. Integrase strand transfer inhibitor-

associated diabetes mellitus: A case report. Int J STD AIDS. 2016 Oct 12. pii: 0956462416675107.
13. Hoffmann C, Welz T, Sabranski M, Kolb M, Wolf E, Stellbrink HJ, Wyen C. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. HIV Med. 2017 Jan;18(1):56-63.
14. Derrick CB, Lu ZK, Caulder CR, Hester EK, Wagner TD, Bookstaver PB. Safety and Tolerability of Stribild in the Southeast United States. J Int Assoc Provid AIDS Care. 2016 Sep;15(5):432-9
15. Ananworanich J, Avihingsanon A. HIV and noncommunicable diseases: the Asian perspective. J Acquir Immune Defic Syndr. 2014 Sep 1;67 Suppl 1:S99-103.
16. Lo YC, Chen MY, Sheng WH, Hsieh SM, Sun HY, Liu WC, Wu PY, Wu CH, Hung CC, Chang SC. Risk factors for incident diabetes mellitus among HIV-infected patients receiving combination antiretroviral therapy in Taiwan: a case-control study. HIV Med. 2009 May;10(5):302-9.
17. Pujari SN, Dravid A, Naik E, Bhagat S, Tash K, Nadler JP, Sinnott JT. Lipodystrophy and dyslipidemia among patients taking first-line, World Health Organization-recommended highly active antiretroviral therapy regimens in Western India. J Acquir Immune Defic Syndr. 2005 Jun 1;39(2):199-202.
18. Choe PG, Choi HJ, Kim NH, et al. High prevalence of low bone mass and associated factors in Korean HIV-positive male patients undergoing antiretroviral therapy. J Int AIDS Soc. 2014;17:18773.
19. Cheung CY, Wong KM, Lee MP, et al. Prevalence of chronic kidney disease in Chinese HIV-infected patients. Nephrol Dial Transplant. 2007;22:3186–3190.
20. Lui G, Wong VW, Wong GL, Chu WC, Wong CK, Yung IM, Wong RY, Yeung SL, Yeung DK, Cheung CS, Chan HY, Chan HL, Lee N. Liver fibrosis and fatty liver in Asian HIV-infected patients. Aliment Pharmacol Ther. 2016 Aug;44(4):411-21.
21. Stewart MW. Human immunodeficiency virus and its effects on the visual system. Infect Dis Rep. 2012;4(1):e25.
22. Tan PB, Hee OK, Cheung C, Yeo TK, Agrawal R, Ng J, et al. Retinal vascular parameter variations in patients with human immunodeficiency virus. Invest Ophthalmol Vis Sci. 2013;54(13):7962-7.
23. van Halsema C, Whitfield T, Lin N, Ashton K, Torkington A, Ustianowski A. Five years' real-life experience with raltegravir in a large HIV centre. Int J STD AIDS. 2016 Apr;27(5):387-93.
24. Todd S, Rafferty P, Walker E, Hunter M, Dinsmore WW, Donnelly CM, McCarty EJ, Quah SP, Emerson CR. Early clinical experience of dolutegravir in an HIV cohort in a larger teaching hospital. Int J STD AIDS. 2017 Jan 1:956462416688127.
25. Sacktor NC, Wong M, Nakasujja N, Skolasky RL, Selnes OA, Musisi S, et al. The International HIV Dementia Scale: a new rapid screening test for HIV dementia. AIDS. 2005;19(13):1367-74.
26. Lui G, Ma RCW, Chook P, Wong CK, Tam CHT, Chan MHM, et al. Progression of Atherosclerosis in HIV-Infected Individuals-Prospective Data From an Asian Cohort. Jaids-Journal of Acquired Immune Deficiency Syndromes. 2017;75(2):198-202.
27. de Ledinghen V, Wong GL, Vergniol J, Chan HL, Hiriart JB, Chan AW, et al. Controlled attenuation parameter for the diagnosis of steatosis in non-alcoholic fatty liver disease. J Gastroenterol Hepatol. 2016;31(4):848-55.

28. Goff DC, Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Sr., Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2935-59.
29. Mocroft A, Lundgren JD, Ross M, Law M, Reiss P, Kirk O, et al. Development and validation of a risk score for chronic kidney disease in HIV infection using prospective cohort data from the D:A:D study. PLoS Med. 2015;12(3):e1001809.
30. Scherzer R, Gandhi M, Estrella MM, Tien PC, Deeks SG, Grunfeld C, et al. A chronic kidney disease risk score to determine tenofovir safety in a prospective cohort of HIV-positive male veterans. AIDS. 2014;28(9):1289-95.
31. American Diabetes Association. Standards of medical care in diabetes – 2017. Diabetes Care. 2017; 40 (Suppl. 1): 1–142.
32. American Diabetes A. 2. Classification and Diagnosis of Diabetes. Diabetes Care. 2017;40(Suppl 1):S11-S24.
33. Keskin M, Kurtoglu S, Kendirci M, Atabek ME, Yazici C. Homeostasis model assessment is more reliable than the fasting glucose/insulin ratio and quantitative insulin sensitivity check index for assessing insulin resistance among obese children and adolescents. Pediatrics. 2005;115(4):e500-3.
34. Whelton PK et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. (2017)
35. Alberti KG, Eckel RH, Grundy SM et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009; 120: 1640e5.
36. Ko GT, Tang J, Chan JC, Sung R, Wu MM, Wai HP, et al. Lower BMI cut-off value to define obesity in Hong Kong Chinese: an analysis based on body fat assessment by bioelectrical impedance. Br J Nutr. 2001;85(2):239-42.
37. Karlas T, Petroff D, Sasso M, Fan JG, Mi YQ, de Ledinghen V, et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. J Hepatol. 2017;66(5):1022-30.
38. Wong VW, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. Hepatology. 2010;51(2):454-62.
39. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1-150.
40. Hall AM, Edwards SG, Lapsley M, et al. Subclnical Tubular Injury in HIV-Infected Individuals on Antiretroviral Therapy: A Cross-sectional Analysis. Am J Kidney Dis 2009;54:1034-42.
41. National Guideline C. ACR Appropriateness Criteria® osteoporosis and bone mineral density. 2016.

42. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56.
43. Serrano-Villar S, Moreno S, Fuentes-Ferrer M, Sanchez-Marcos C, Avila M, Sainz T, et al. The CD4:CD8 ratio is associated with markers of age-associated disease in virally suppressed HIV-infected patients with immunological recovery. HIV Med. 2014;15(1):40-9.
44. Ofotokun I, Na LH, Landovitz RJ, Ribaudo HJ, McComsey GA, Godfrey C, Aweeka F, Cohn SE, Sagar M, Kuritzkes DR, Brown TT, Patterson KB, Para MF, Leavitt RY, Villasis-Keever A, Baugh BP, Lennox JL, Currier JS; AIDS Clinical Trials Group (ACTG) A5257 Team. Comparison of the metabolic effects of ritonavir-boosted darunavir or atazanavir versus raltegravir, and the impact of ritonavir plasma exposure: ACTG 5257. Clin Infect Dis. 2015 Jun 15;60(12):1842-51.
45. Lemeshow, S., Hosmer Jr., D.W., Klar, J.,and Lwanga S.K. Adequacy of Sample Size in Health Studies. WHO, 1990.