

## **1 Online Supplementary Material**

### ***1.1 Measurement of renal function in patients with HIV-1 infection***

Glomerular function has been assessed using various measures in numerous studies in patients with HIV infection [1-19]. The gold standard for determining glomerular filtration rate (GFR) is isotopic measurement; however, this technique is invasive, time-consuming and requires specialist techniques. In clinical practice, GFR is approximated by using serum creatinine-based equations such as the CG equation, which provides an estimate of creatinine clearance (eCC) adjusted for age, gender, and body weight [20], or the MDRD [21], MDRD-4 [22] or CKD-EPI equations [23], which provide an estimate of GFR (eGFR) adjusted for differences by age, race, gender and body size. However, measurements of serum creatinine can vary up to 15% between laboratories [24], which has prompted the recommendation to use isotope-dilution mass spectrometry (IDMS) standardisation of serum creatinine measurements in order to reduce this variability [25]. The CG [20] and original MDRD [21] equations were validated using non-standardised serum creatinine measurements, whereas the updated MDRD-4 [22] and the CKD-EPI equations [23] are validated for use with IDMS standardised measurements.

Beyond laboratory issues, other factors limit the predictive performance of creatinine-based estimating equations. The rate at which creatinine is produced is dependent on muscle mass, which is not fully accounted for in the creatinine-based methods, and is especially relevant in the current context as HIV-related muscle wasting may affect serum creatinine levels [26-28]. Ingestion of high quantities of meat [29], creatine containing supplements [30] or drugs that inhibit proximal tubular secretion of creatinine, such as cobicistat, ritonavir and trimethoprim, can also increase creatinine levels in the serum [31-33].

The CKD-EPI equation provides more precise results, particularly if the GFR is  $\geq 60$  mL/min [6, 34, 35], whereas the MDRD equation is more sensitive if eGFR is  $< 60$  mL/min [36].

CKD-EPI equations are generally more accurate than the CG or MDRD equations in HIV-infected individuals with normal or deteriorating renal function [2, 6, 12, 26, 34].

More recently, cystatin C levels or GFR estimating equations based upon cystatin C have been evaluated as a measure of renal function in patients with HIV because cystatin C is not appreciably influenced by muscle mass, diet, or tubular secretion of creatinine [28]. Cystatin C measurements correlated with isotopic GFR in clinical studies of patients with HIV infection in which this method was a better predictor of GFR than the CKD-EPI, MDRD and CG equations [2, 12], although this was not shown in one small observational study [1] and two further observational studies using iohexol [35] and isotopic GFR measurement [36] as gold standards. Although a large meta-analytic study comparing the performance of creatinine-based versus cystatin C-based equations in diverse populations with and without renal disease suggested that cystatin C-based or combined creatinine and cystatin C-based equations improved the accuracy of classification for the subsequent outcomes of mortality or end-stage renal disease (ESRD) [37], it appears that cystatin C-based methods do not confer advantages over creatinine-based methods in patients with HIV infection [6, 28, 35, 36], especially because cystatin-C is elevated in untreated HIV infection [38]. A useful summary of all currently available GFR estimating equations is available in the following website:

[nephron.com/GFR\\_equations.html](http://nephron.com/GFR_equations.html)

## References

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## 1.2 Search strategy

### 1.2.1 PubMed Strategy

| Search | Add to builder | Query                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|--------|----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| #01    | Add            | Search (((hiv infection[MeSH Terms]) OR HIV[MeSH Terms]) OR HIV infection) OR human immunodeficiency virus                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| #02    | Add            | Search (((((((agents, antiretroviral[MeSH Terms]) OR antiretroviral therapy, highly active[MeSH Terms]) OR protease inhibitor[MeSH Terms]) OR Antiretroviral*) OR ARV) OR antiretroviral therap*) OR anti-retroviral therap*) OR protease inhibitor*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| #03    | Add            | Search (((((((((((saquinavir[MeSH Terms]) OR ritonavir[MeSH Terms]) OR indinavir[MeSH Terms]) OR nelfinavir[MeSH Terms]) OR lopinavir[MeSH Terms]) OR saquinavir) OR ritonavir) OR indinavir) OR nelfinavir) OR lopinavir) OR fosamprenavir) OR tipranavir) OR darunavir) OR amprenavir) OR atazanavir                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| #04    | Add            | Search (#2 or #3)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| #05    | Add            | Search ((ritonavir-boosted) OR RTV-boosted) AND (tenofovir OR TDF)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| #06    | Add            | Search (#4 or #5)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| #07    | Add            | Search ((Renal Insufficiency, Chronic OR Kidney Diseases OR Renal Insufficiency OR Renal Replacement Therapy OR Kidney Transplantation OR Glomerular Filtration Rate OR iothexol OR inulin OR creatinine OR nephrolithiasis OR nephrology OR proteinuria OR Nephritis, Interstitial OR Renal Dialysis OR Peritoneal dialysis[MeSH Terms])) OR (Chronic kidney disease* OR CKD Chronic renal disease* OR kidney disease* OR renal disease* OR Renal Insufficienc* OR Kidney failure OR renal failure OR Renal function OR kidney function OR Renal Replacement Therapy OR Kidney Transplantation OR renal transplantation OR estimated glomerul* filtration rate* OR eGFR OR measured glomerul* filtration rate* OR GFR OR iothexol OR inulin OR creatinine OR nephrolithiasis OR nephrology OR proteinuria OR interstitial nephritis OR tubular dysfunction OR Hemodialysis OR Renal Dialysis OR Peritoneal dialysis OR MDRD OR "Modification of Diet in Renal Disease" OR CKD-Epi OR "Chronic Kidney Disease Epidemiology Collaboration equation" OR Cockcroft-Gault OR "Urine albumin creatinine ratio" OR "Urinary albumin creatinine ratio" OR "Urine albumin:creatinine ratio" OR "Urinary albumin:creatinine ratio" OR "Urine albumin : creatinine ratio" OR "Urinary albumin : creatinine ratio" OR "Urine albumin-to-creatinine ratio" OR "Urinary albumin-to-creatinine ratio" OR "Urinary protein creatinine ratio" OR "Urine protein:creatinine ratio" OR "Urinary protein:creatinine ratio" OR "Urine protein : creatinine ratio" OR "Urinary protein : creatinine ratio" OR "Urine protein-to-creatinine ratio" OR "Urinary protein-to-creatinine ratio") |
| #08    | Add            | Search (((hypertension OR diabetes mellitus OR aging[MeSH Terms])) OR (hypertension OR diabetes mellitus OR aging OR ageing OR HCV co-infection OR HBV co-infection OR hepatitis C co-infection OR hepatitis B co-infection)) AND kidney disease[MeSH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

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|     |     | Terms]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| #09 | Add | Search (((Substance Abuse, Intravenous OR Drug Users[MeSH Terms])) OR ("intravenous drug abuse" OR "intravenous substance abuse")) AND kidney diseases[MeSH Terms]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| #10 | Add | Search (#7 or #8 or #9)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| #11 | Add | Search (#1 AND #6 AND #10)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| #12 | Add | Search ("2003"[Date - Entrez] : "2013"[Date - Entrez])                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| #13 | Add | Search (#11 AND #12)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| #14 | Add | Search (#13) Filters: English                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| #15 | Add | Search (addresses or autobiography or bibliography or biography or comment or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or duplicate publication or editorial or festschrift or government publications or guideline or in vitro or interactive tutorial or interview or lectures or legal cases or legislation or letter or news or newspaper article or overall or patient education handout or periodical index or portraits or practice guideline or published erratum or "research support, american recovery and reinvestment act" or retracted publication or "retraction of publication" or technical report or video-audio media or webcasts) |
| #16 | Add | Search (#14 NOT #15)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| #17 | Add | Search (#14 NOT #15) Filters: Humans                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

### 1.2.2 Embase strategy

| #  | Searches                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1  | *Human immunodeficiency virus/ or *Human immunodeficiency virus infection/ or HIV infection\$.tw. or human immunodeficiency virus.tw.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 2  | *antiretrovirus agent/ or *proteinase inhibitor/ or *highly active antiretroviral therapy/ or *antiretrovirus agent/ or *anti human immunodeficiency virus agent/ or (Antiretroviral\$ or ARV or antiretroviral therap\$ or anti-retroviral therap\$ or protease inhibitor\$).tw.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 3  | *Saquinavir/ or *Ritonavir/ or *Indinavir/ or *Nelfinavir/ or *Lopinavir/ or *Tipranavir/ or *darunavir/ or *amprenavir/ or *atazanavir/ or *fosamprenavir/ or (saquinavir or ritonavir or indinavir or nelfinavir or lopinavir or fosamprenavir or tipranavir or darunavir or amprenavir or atazanavir).tw.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 4  | ((ritonavir-boosted or RTV-boosted) and (tenofovir or TDF)).tw.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 5  | 2 or 3 or 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 6  | 1 and 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 7  | *kidney failure/ or *Kidney Disease/ or *Renal Replacement Therapy/ or *Kidney Transplantation/ or *Glomerulus Filtration Rate/ or *iohexol/ or *inulin/ or *creatinine/ or *creatinine blood level/ or *nephrolithiasis/ or *nephrology/ or *proteinuria/ or *interstitial nephritis/ or *hemodialysis/ or *Peritoneal dialysis/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 8  | (Chronic kidney disease\$ or CKD or Chronic renal disease\$ or kidney disease\$ or renal disease\$ or Renal Insufficienc\$ or Kidney failure or renal failure or Renal function or kidney function or Renal Replacement Therapy or Kidney Transplantation or renal transplantation or estimated glomerul\$ filtration rate\$ or eGFR or measured glomerul\$ filtration rate\$ or GFR or iohexol or inulin or creatinine or nephrolithiasis or nephrology or proteinuria or interstitial nephritis or tubular dysfunction or Hemodialysis or Renal Dialysis or Peritoneal dialysis or MDRD or Modification of Diet in Renal Disease or CKD-Epi or Chronic Kidney Disease Epidemiology Collaboration equation or Cockcroft-Gault or (albumin adj2 creatinine) or albumin:creatinine or (protein adj2 creatinine) or protein:creatinine).tw. |
| 9  | (*hypertension/ or hypertension.tw. or *Diabetes mellitus/ or Diabetes mellitus.tw. or *Aging/ or ag?ing.tw. or HCV co-infection.tw. or HBV co-infection.tw. or hepatitis C co-infection.tw. or hepatitis B co-infection.tw.) and *Kidney Disease/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 10 | (*"drug use"/ or *Substance Abuse/ or *intravenous drug abuse/ or intravenous drug abuse.tw. or intravenous substance abuse.tw.) and *Kidney Disease/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 11 | 7 or 8 or 9 or 10                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 12 | 6 and 11                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 13 | limit 12 to (human and english language and yr="2003 - 2013")                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 14 | limit 13 to (book or book series or conference proceeding or "conference review" or editorial or erratum or letter or note or report or short survey or trade journal)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 15 | 13 not 14                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 16 | remove duplicates from 15                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |